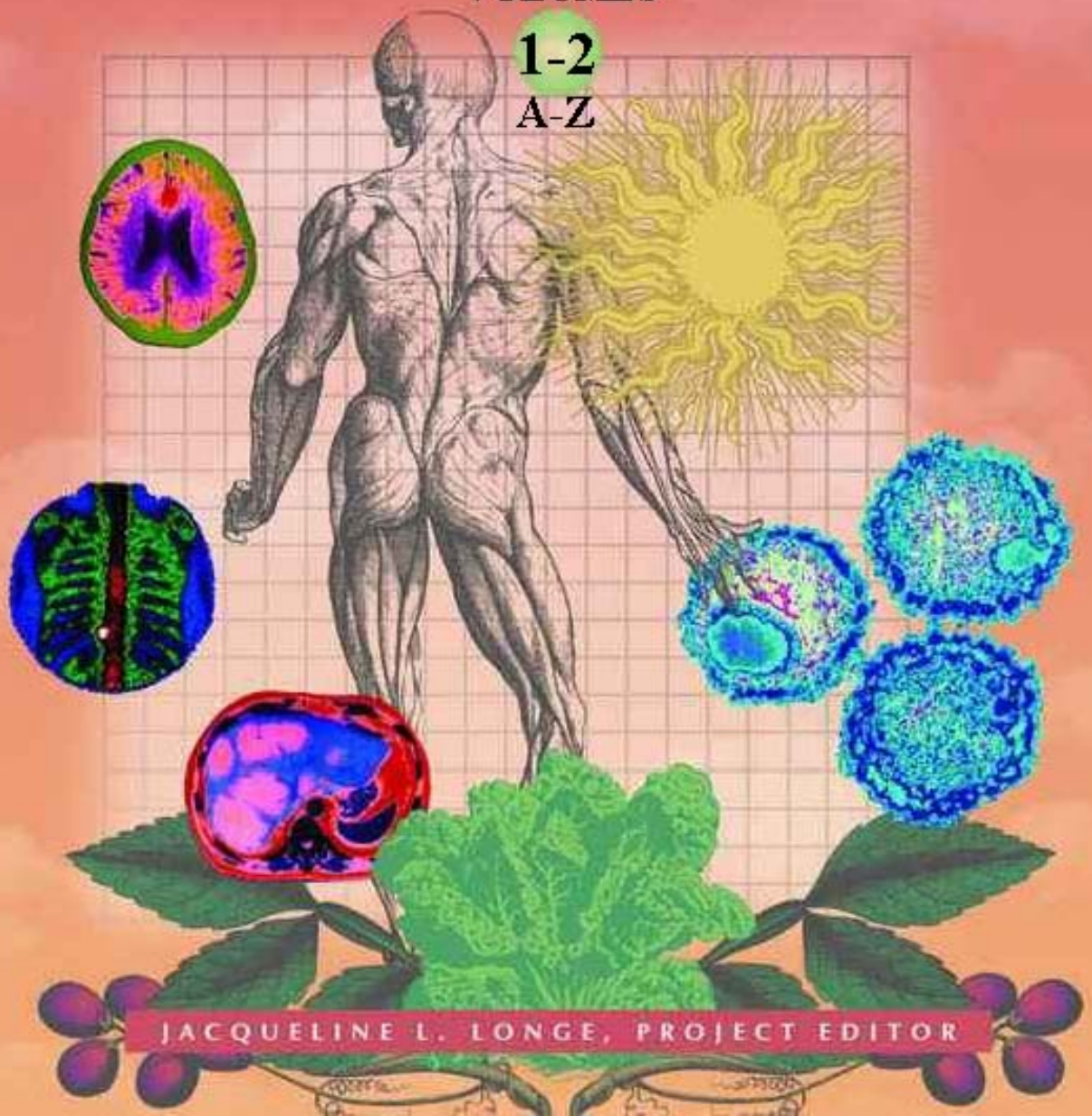
The GALE ENCYCLOPEDIA of CANCER

A GUIDE TO CANCER AND ITS TREATMENTS

SECOND EDITION

VOLUMES
1-2
A-Z



JACQUELINE L. LONGE, PROJECT EDITOR

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VOLUME

1

A-K

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THOMSON GALE

Detroit • New York • San Francisco • San Diego • New Haven, Conn. • Waterville, Maine • London • Munich

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2

L-Z
GENERAL INDEX

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The Gale Encyclopedia of Cancer: A Guide to Cancer and Its Treatments, Second Edition

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PLEASE READ—IMPORTANT INFORMATION

The *Gale Encyclopedia of Cancer* is a medical reference product designed to inform and educate readers about a wide variety of cancers, treatments, diagnostic procedures, side effects, and cancer drugs. The Gale Group believes the product to be comprehensive, but not necessarily definitive. It is intended to supplement, not replace, consultation with a physician or other health care practitioner. While the Gale Group has made substantial efforts to provide information that is accurate, comprehensive, and up-to-date, the Gale Group makes no representations or warranties of any kind, including without limitation, warranties of merchantability or fitness for a particular purpose, nor does it guarantee the accuracy, comprehensiveness, or timeliness of the information contained in this product. Readers should be aware that the universe of medical knowledge is constantly growing and changing, and that differences of medical opinion exist among authorities. Readers are also advised to seek professional diagnosis and treatment for any medical condition, and to discuss information obtained from this book with their health care provider.

INTRODUCTION

The *Gale Encyclopedia of Cancer: A Guide to Cancer and Its Treatments* is a unique and invaluable source of information for anyone touched by cancer. This collection of over 450 entries provides in-depth coverage of specific cancer types, diagnostic procedures, treatments, cancer side effects, and cancer drugs. In addition, entries have been included to facilitate understanding of common cancer-related concepts, such as cancer biology, carcinogenesis, and cancer genetics, as well as cancer issues such as clinical trials, home health care, fertility issues, and cancer prevention.

This encyclopedia minimizes medical jargon and uses language that laypersons can understand, while still providing thorough coverage that will benefit health science students as well.

Entries follow a standardized format that provides information at a glance. Rubrics include:

Cancer types

- Definition
- Description
- Demographics
- Causes and symptoms
- Diagnosis
- Treatment team
- Clincial staging, treatments, and prognosis
- Coping with cancer treatment
- Clinical trials
- Prevention
- Special concerns
- Resources
- Key terms

Cancer drugs

- Definition
- Purpose
- Description
- Recommended dosage
- Precautions
- Side effects
- Interactions

INCLUSION CRITERIA

A preliminary list of cancers and related topics was compiled from a wide variety of sources, including professional medical guides and textbooks, as well as consumer guides and encyclopedias. The advisory board, made up of medical doctors and oncology pharmacists, evaluated the topics and made suggestions for inclusion. Final selection of topics to include was made by the advisory board in conjunction with the Thomson Gale editor.

ABOUT THE CONTRIBUTORS

The essays were compiled by experienced medical writers, including physicians, pharmacists, nurses, and other health care professionals. The advisors reviewed the completed essays to ensure that they are appropriate, up-to-date, and medically accurate.

HOW TO USE THIS BOOK

The *Gale Encyclopedia of Cancer* has been designed with ready reference in mind.

- Straight **alphabetical arrangement** of topics allows users to locate information quickly.
- **Bold-faced terms** within entries direct the reader to related articles.
- **Cross-references** placed throughout the encyclopedia direct readers from alternate names and related topics to entries.
- A list of **key terms** is provided where appropriate to define unfamiliar terms or concepts.
- A list of **questions to ask the doctor** is provided whevever appropriate to help facilitate discussion with the patient's physician.

- The **Resources** section for non-drug entries directs readers to additional sources of medical information on a topic.
- Valuable **contact information** for organizations and support groups is included with each cancer type entry. The appendices at the back of Volume 2 contain extensive lists of organizations arranged in alphabetical order.
- A comprehensive **general index** guides readers to all topics mentioned in the text.
- A note about **drug entries**: Drug entries are listed in alphabetical order by common **generic names**. However, because many oncology drugs have more than one common generic name, and because in many cases, the brand name is also often used interchangeably with a generic name, drugs can be located in one of three ways. The reader can: find the generic drug name in alphabetical order, be directed to the entry from an alternate name cross-reference, or the reader can use the **index** to look up a **brand name**, which will direct the reader to the equivalent generic name entry. If the reader would like more information about oncology drugs than these entries provide, the reader is encouraged to consult with a physician, pharmacist, or the reader may find helpful any one of a number of books about cancer drugs. Two that may be helpful are: D. Solimando's *Drug Information Handbook for Oncology*, or R. Ellerby's *Quick Reference Handbook of Oncology Drugs*.

GRAPHICS

The *Gale Encyclopedia of Cancer* contains over 200 full-color illustrations, photos and tables. Eleven illustrations of various body systems can be found in the front matter of the book, and these can help the reader to understand which cancers may affect which organs, and how the various systems interact.

PHOTO ACKNOWLEDGMENTS

On the cover, clockwise from upper left:

- Colored computed tomography (CT) scan of a human brain. (Dept. of Clinical Radiology, Salisbury District Hospital, Science Source/Photo Researchers. Reproduced by permission.)
- Color digitized image of the herpes simplex virus. (Custom Medical Stock Photo. Reproduced by permission.)
- Colored CT scan revealing cancer of the liver. (Dept. of Clinical Radiology, Salisbury District Hospital, Science Source/Photo Reseachers. Reproduced by permission.)
- False-color bone scan of the spine and ribs showing metastatic bone cancer of the spine. (CNRI, Science Source/Photo Researchers. Reproduced by permission.)

FOREWORD

Unfortunately, man must suffer disease. Some diseases are totally reversible and can be effectively treated. Moreover, some diseases with proper treatment have been virtually annihilated, such as polio, rheumatic fever, smallpox, and, to some extent, tuberculosis. Other diseases seem to target one organ, such as the heart, and there has been great progress in either fixing defects, adding blood flow, or giving medications to strengthen the diseased pump. Cancer, however, continues to frustrate even the cleverest of doctors or the most fastidious of health conscious individuals. Why?

By its very nature, cancer is a survivor. It has only one purpose: to proliferate. After all, that is the definition of cancer: unregulated growth of cells that fail to heed the message to stop growing. Normal cells go through a cycle of division, aging, and then selection for death. Cancer cells are able to circumvent this normal cycle, and escape recognition to be eliminated.

There are many mechanisms that can contribute to this unregulated cell growth. One of these mechanisms is inheritance. Unfortunately, some individuals can be programmed for cancer due to inherited disorders in their genetic makeup. In its simplest terms, one can inherit a faulty gene or a missing gene whose role is to eliminate damaged cells or to prevent imperfect cells from growing. Without this natural braking system, the damaged cells can divide and lead to more damaged cells with the same abnormal genetic makeup as the parent cells. Given enough time, and our inability to detect them, these groups of cells can grow to a size that will cause discomfort or other symptoms.

Inherited genetics are obviously not the only source of abnormalities in cells. Humans do not live in a sterile world devoid of environmental attacks or pathogens. Humans must work, and working environments can be dangerous. Danger can come in the form of radiation, chemicals, or fibers to which we may be chronically exposed with or without our knowledge. Moreover, man must eat, and if our food is contaminated with these environmental hazards, or if we prepare our food in a way that may change the chemical nature of the food to hazardous molecules, then chronic exposure to these toxins could damage cells. Finally, man is social. He has found certain habits which are pleasing to him because they either relax him or release his inhibitions. Such habits, including smoking and alcohol consumption, can have a myriad of influences on the genetic makeup of cells.

Why the emphasis on genes in the new century? Because they are potentially the reason as well as the answer for cancer. Genes regulate our micro- and macroscopic events by eventually coding for proteins that control our structure and function. If the above-mentioned environmental events cause errors in those genes that control growth, then imperfect cells can start to take root. For the majority of cases, a whole cascade of genetic events must occur before a cell is able to outlive its normal predecessors. This cascade of events could take years to occur, in a silent, undetected manner until the telltale signs and symptoms of advanced cancer are seen, including pain, lack of appetite, cough, loss of blood, or the detection of a lump. How did these cells get to this state where they are now dictating the everyday physical, psychological, and economic events for the person afflicted?

At this time, the sequence of genetic catastrophes is much too complex to comprehend or summarize because, it is only in the past year that we have even been able to map what genes we have and where they are located in our chromosomes. We have learned, however, that cancer cells are equipped with a series of self-protection mechanisms. Some of the altered genes are actually able to express themselves more than in the normal situation. These genes could then code for more growth factors for the transforming cell, or they could make proteins that could keep our own immune system from eliminating these interlopers. Finally, these cells are chameleons: if we treat them with drugs to try to kill them, they can "change their colors" by mutation, and then be resistant to the drugs that may have harmed them before.

Then what do we do for treatment? Man has always had a fascination with grooming, and grooming involves

removal—dirt, hair, waste. The ultimate removal involves cutting away the spoiled or imperfect portion. An abnormal growth? Remove it by surgery... make sure the edges are clean. Unfortunately, the painful reality of cancer surgery is that it is highly effective when performed in the early stages of the disease. ''Early stages of the disease'' implies that there is no spread, or, hopefully, before there are symptoms. In the majority of cases, however, surgery cannot eradicate all the disease because the cancer is not only at the primary site of the lump, but has spread to other organs. Cancer is not just a process of growth, but also a metastasizing process that allows for invasion and spread. The growing cells need nourishment so they secrete proteins that allow for the growth of blood vessels (angiogenesis); once the blood vessels are established from other blood vessels, the tumor cells can make proteins that will dissolve the imprisoning matrix surrounding them. Once this matrix is dissolved, it is only a matter of time before thecancer cells will migrate to other places making the use of surgery fruitless.

Since cancer cells have a propensity to leave home and pay a visit to other organs, therapies must be geared to treat the whole body and not just the site of origin. The problem with these chemotherapies is that they are not selective and wreak havoc on tissues that are not affected by the cancer. These therapies are not natural to the human host, and result in nausea, loss of appetite, fatigue, as well as a depletion in our cells that protect us from infection and those that carry oxygen. Doctors who prescribe such medications walk a fine line between helping the patient (causing a ''response'' in the cancer by making it smaller) or causing ''toxicity'' which, due to effects on normal organs, causes the patient problems. Although these drugs are far from perfect, we are fortunate to have them because when they work, their results can be remarkable.

But that's the problem—''when they work.'' We cannot predict who is going to benefit from our therapies, and doctors must inform the patient and his/her family about countless studies that have been done to validate the use of these potentially beneficial/potentially harmful agents. Patients must suffer the frustration that oncologists have because each individual afflicted with cancer is different, and indeed, each cancer is different. This makes it virtually impossible to personalize an individual's treatment expectations and life expectancy. Cancer, after all, is a very impersonal disease, and does not respect sex, race, wealth, age, or any other ''human'' characteristics.

Cancer treatment is in search of ''smart'' options. Like modern-day instruments of war, successful cancer treatment will necessitate the construction of therapies which can do three basic tasks: search out the enemy, recognize the enemy, and kill the enemy without causing ''friendly fire.'' The successful therapies of the future will involve the use of ''living components,'' ''manufactured components,'' or a combination of both. Living components, white blood cells, will be educated to recognize where the cancer is, and help our own immune system fight the foreign cells. These lymphocytes can be educated to recognize signals on the cancer cell which make them unique. Therapies in the future will be able to manufacture molecules with these signature, unique signals which are linked to other molecules specifically for killing the cells. Only the cancer cells are eliminated in this way, hopefully sparing the individual from toxicity.

Why use these unique signals as delivery mechanisms? If they are unique and are important for growth of the cancer cell, why not target them directly? This describes the ambitious mission of gene therapy, whose goal is to supplement a deficient, necessary genetic pool or diminish the number of abnormally expressed genes fortifying the cancer cells. If a protein is not being made that slows the growth of cells, gene therapy would theoretically supply the gene for this protein to replenish it and cause the cells to slow down. If the cells can make their own growth factors that sustain them selectively over normal cells, then the goal is to block the production of this growth factor. There is no doubt that gene therapy is the wave of the future and is under intense investigation and scrutiny at present. The problem, however, is that there is no way to tell when this future promise will be fulfilled.

No book can describe the medical, psychological, social, and economic burden of cancer, and if this is your first confrontation with the enemy, you may find yourself overwhelmed with its magnitude. Books are only part of the solution. Newly enlisted recruits in this war must seek proper counsel from educated physicians who will inform the family and the patient of the risks and benefits of a treatment course in a way that can be understood. Advocacy groups of dedicated volunteers, many of whom are cancer survivors, can guide and advise. The most important component, however, is an intensely personal one. The afflicted individual must realize that he/she is responsible for charting the course of his/her disease, and this requires the above described knowledge as well as great personal intuition. Cancer comes as a series of shocks: the symptoms, the diagnosis, and the treatment. These shocks can be followed by cautious optimism or profound disappointment. Each one of these shocks either reinforces or chips away at one's resolve, and how an individual reacts to these issues is as unique as the cancer that is being dealt with.

While cancer is still life-threatening, strides have been made in the fight against the disease. Thirty years ago, a young adult diagnosed with testicular cancer had

few options for treatment that could result in cure. Now, chemotherapy for good risk Stage II and III testicular cancer can result in a complete response of the tumor in 98% of the cases and a durable response in 92%. Sixty years ago, there were no regimens that could cause a complete remission for a child diagnosed with leukemia; but now, using combination chemotherapy, complete remissions are possible in 96% of these cases. Progress has been made, but more progress is needed. The first real triumph in cancer care will be when cancer is no longer thought of as a life-ending disease, but as a chronic disease whose symptoms can be managed. Anyone who has been touched by cancer or who has been involved in the fight against it lives in hope that that day will arrive.

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A number of experts in the medical community provided invaluable assistance in the formulation of this encyclopedia. The advisory board performed a myriad of duties, from defining the scope of coverage to reviewing individual entries for accuracy and accessibility. The editor would like to express appreciation to them for their time and for their contributions.

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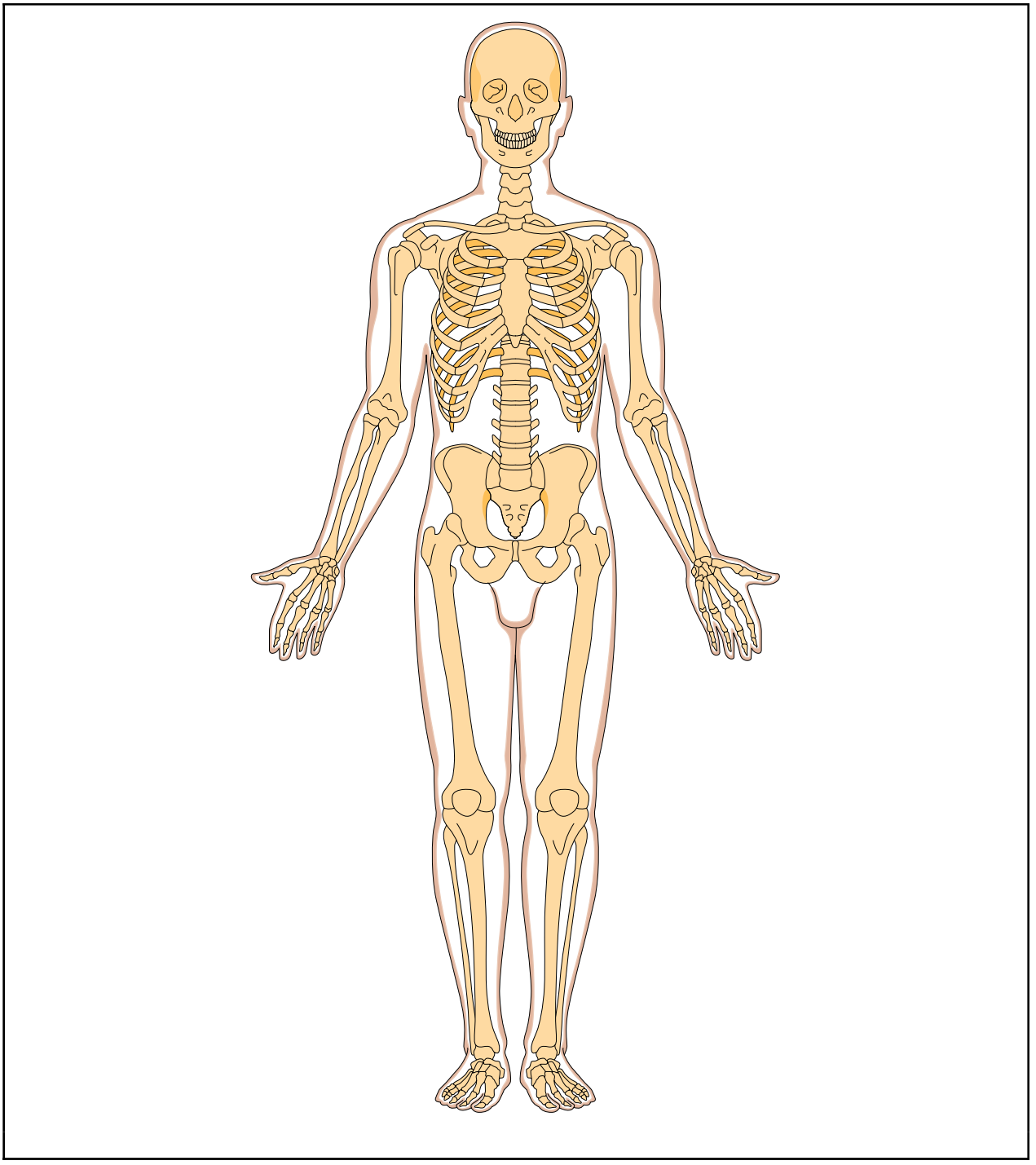
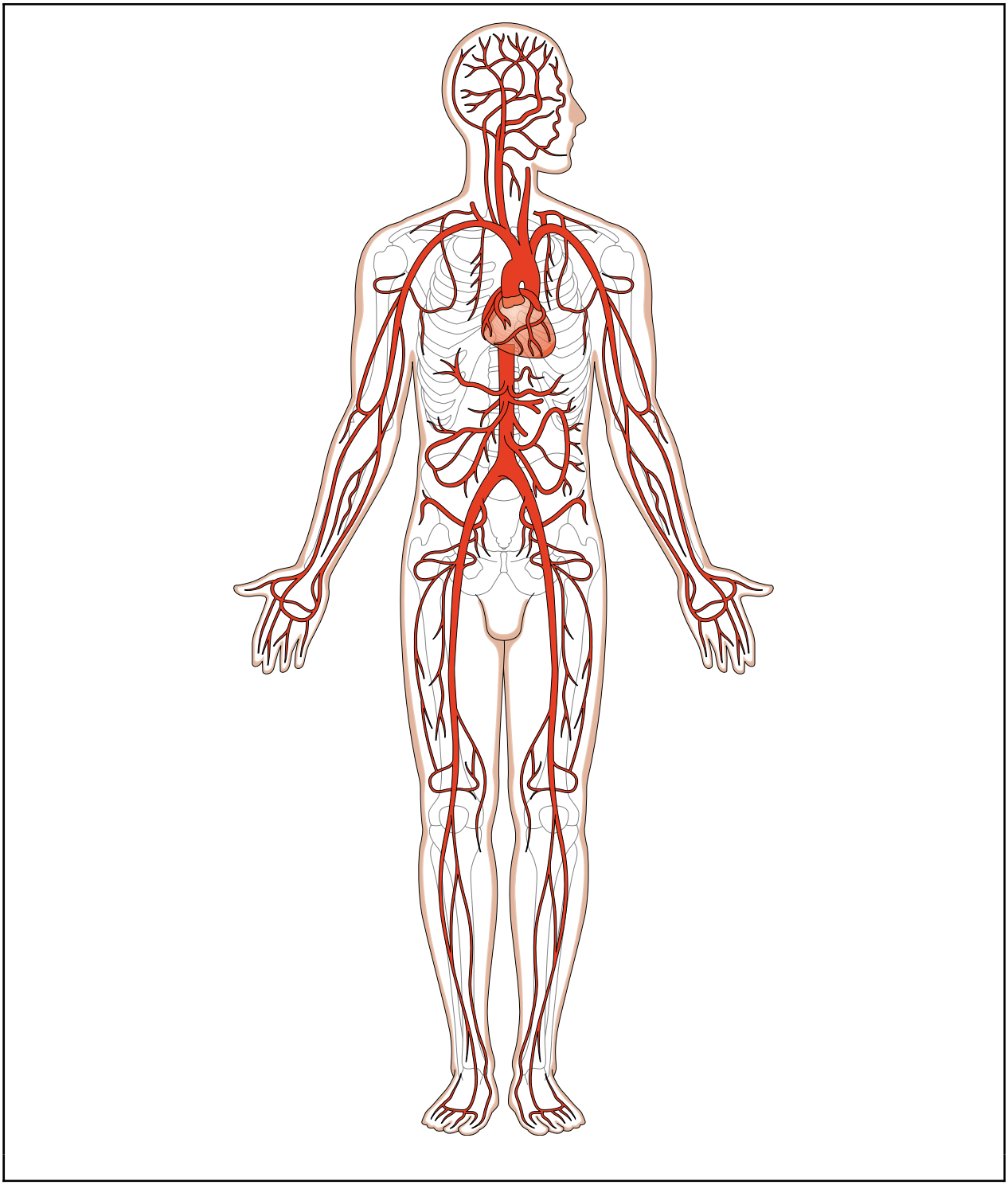
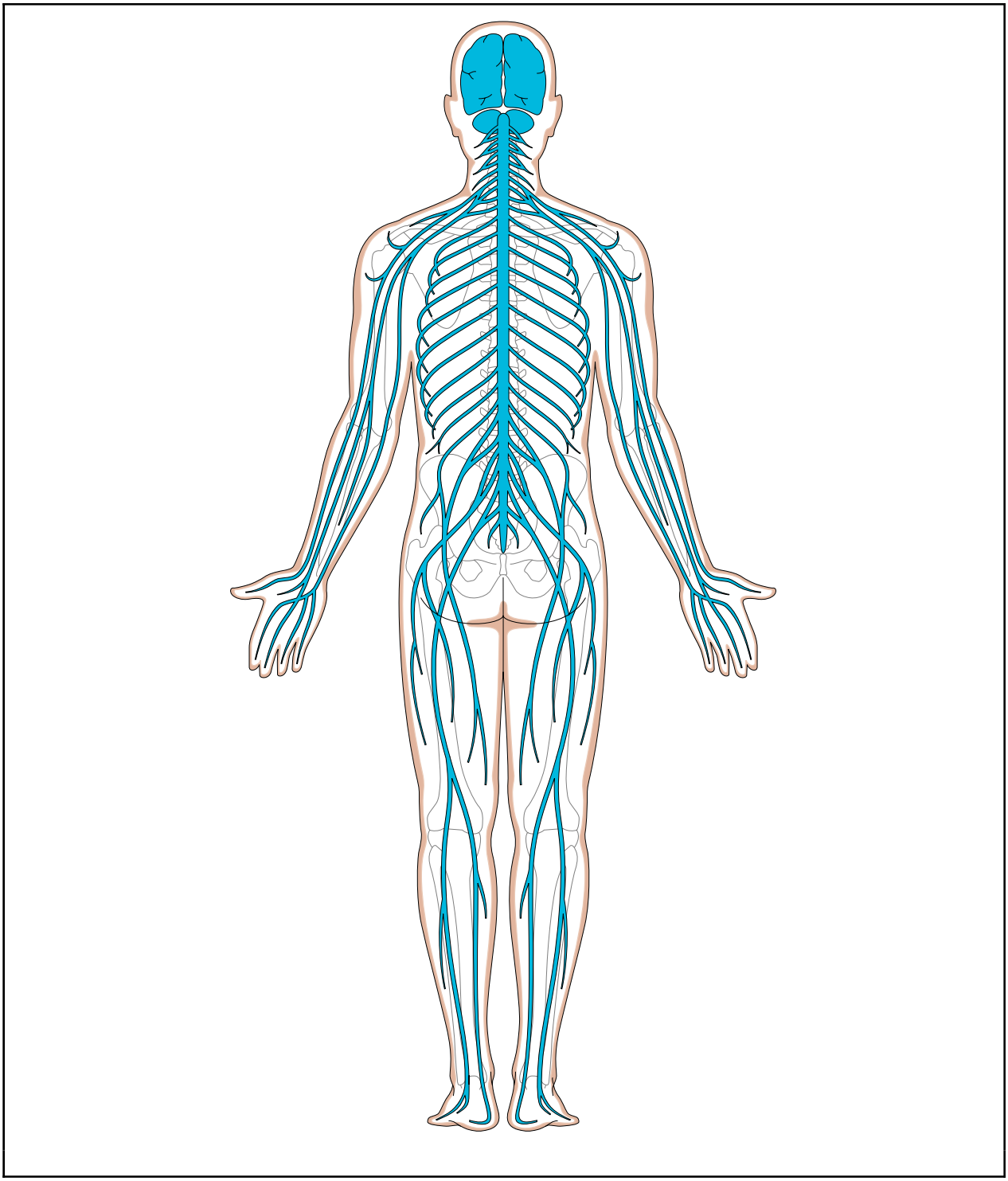


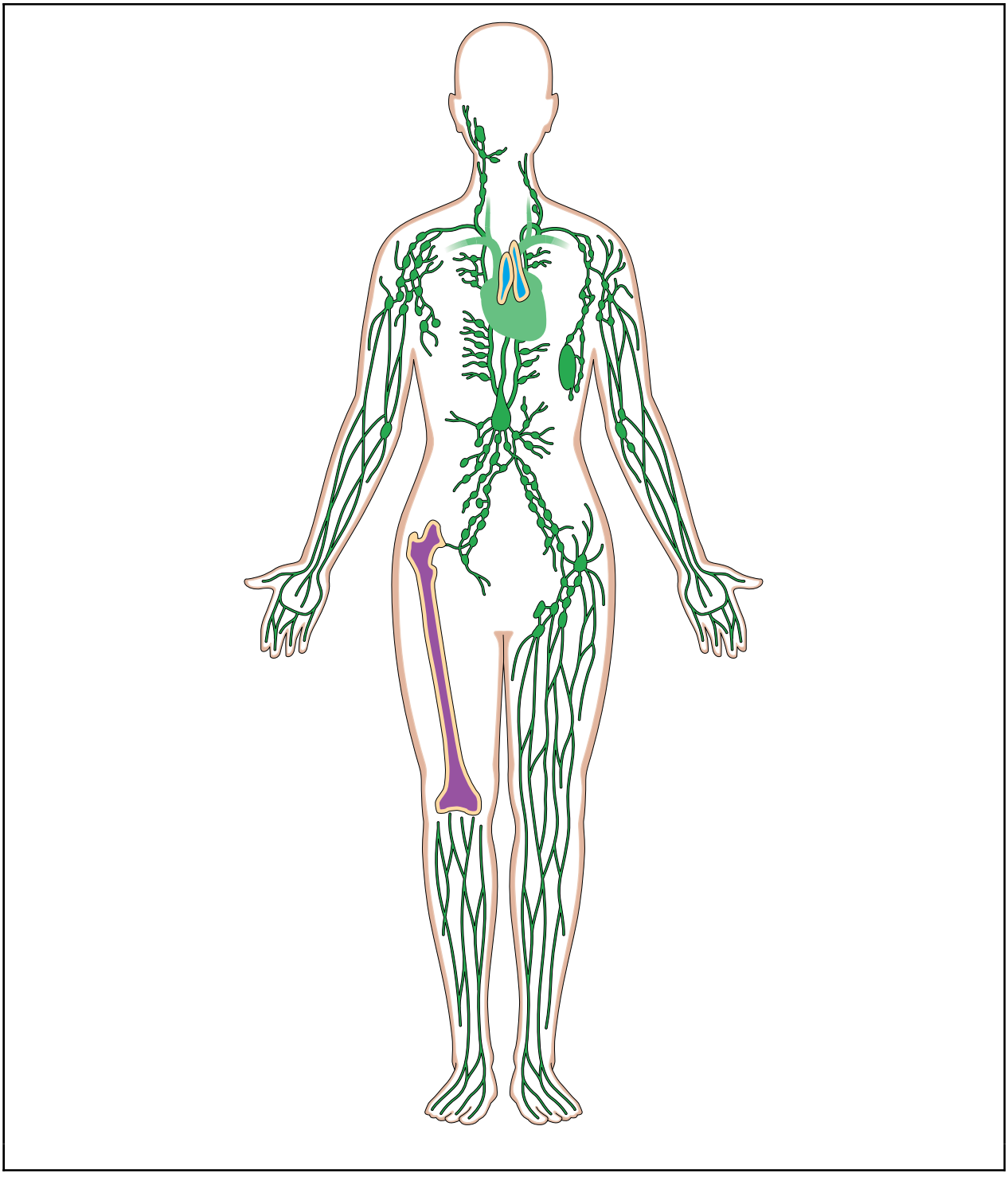
HUMAN SKELETON and SKIN. Some cancers that affect the skeleton are: Osteosarcoma; Ewing's sarcoma; Fibrosarcoma (can also be found in soft tissues like muscle, fat, connective tissues, etc.). Some cancers that affect tissue near bones: Chondrosarcoma (affects joints near bones); Rhabdomyosarcoma (formed from cells of muscles attached to bones); Malignant fibrous histiocytoma (common in soft tissues, rare in bones). SKIN CANCERS: Basal cell carcinoma; Melanoma; Merkel cell carcinoma; Squamous cell carcinoma of the skin; and Trichilemmal carcinoma. Precancerous skin condition: Bowen's disease. Lymphomas that affect the skin: Mycosis fungoides; Sézary syndrome. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*



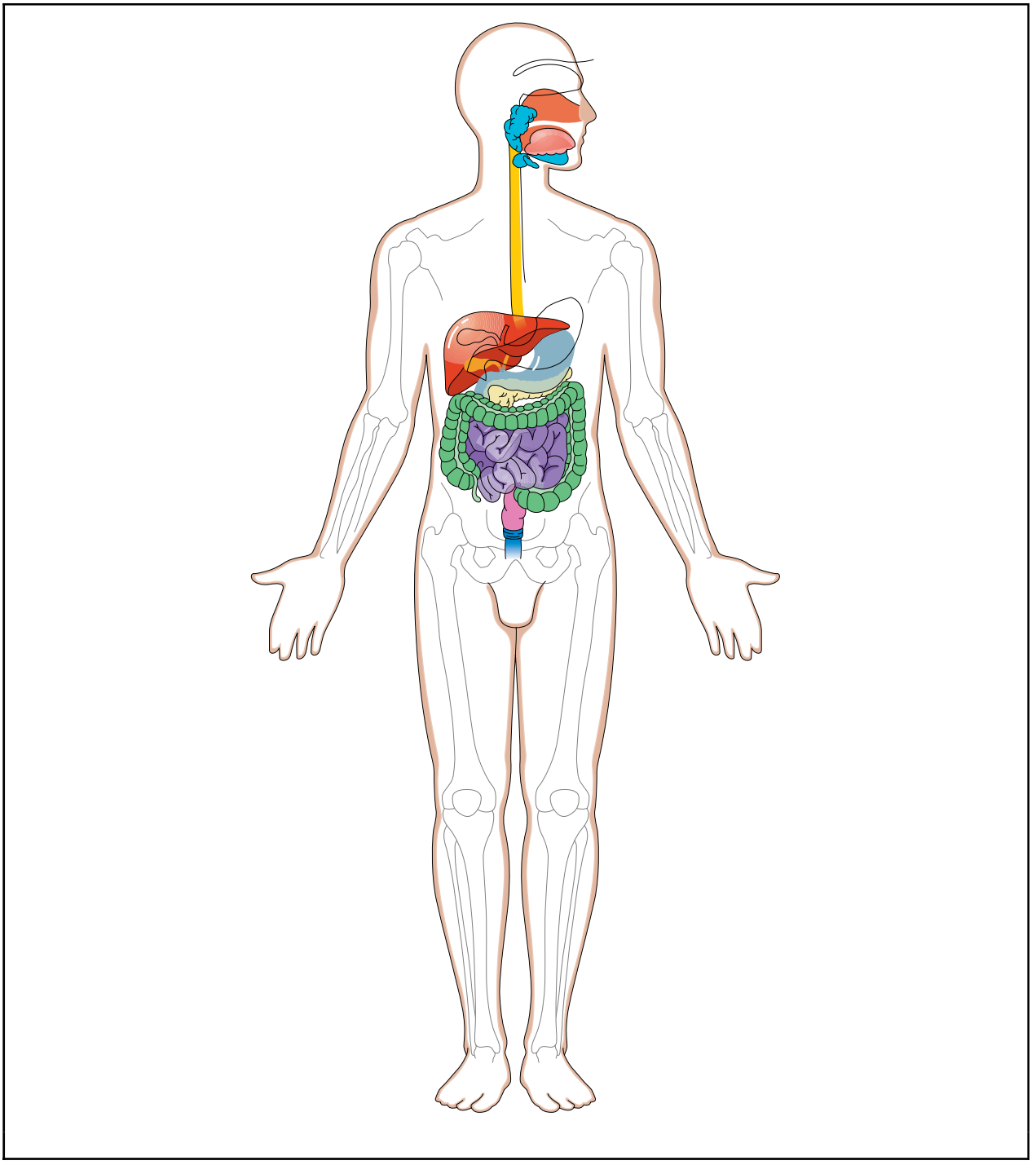
HUMAN CIRCULATORY SYSTEM. Some cancers of the blood cells are: Acute erythroblastic leukemia; Acute lymphocytic leukemia; Acute myelocytic leukemia; Chronic lymphocytic leukemia; Chronic myelocytic leukemia; Hairy cell leukemia; and Multiple myeloma. One condition associated with various cancers that affects blood is called Myelofibrosis. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*



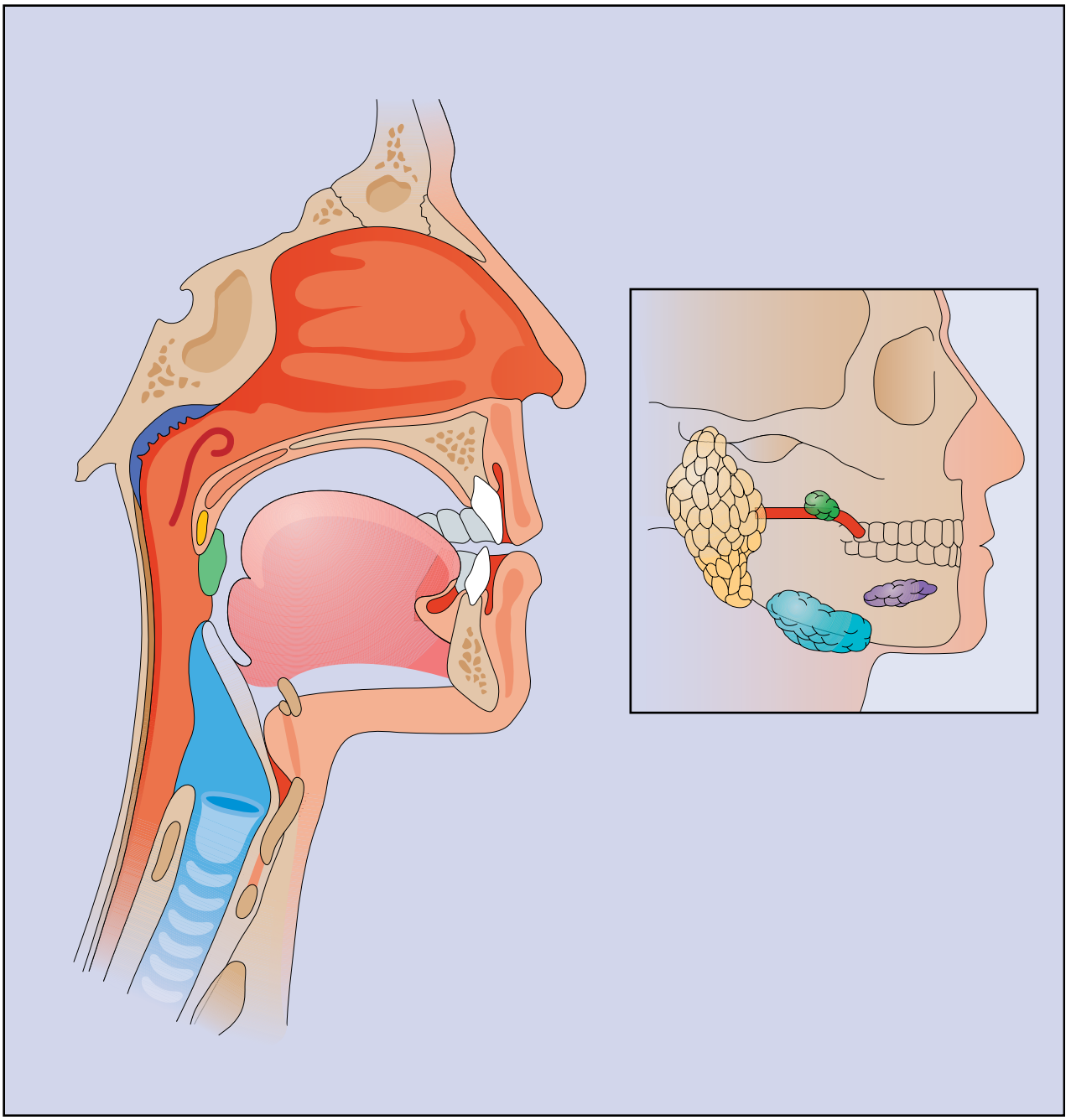
HUMAN NERVOUS SYSTEM. Some brain and central nervous system tumors are: Astrocytoma; Carcinomatous meningitis; Central nervous system carcinoma; Central nervous system lymphoma; Chordoma; Choroid plexus tumors; Craniopharyngioma; Ependymoma; Medulloblastoma; Meningioma; Oligodendroglioma; and Spinal axis tumors. One kind of noncancerous growth in the brain: Acoustic neuroma. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*



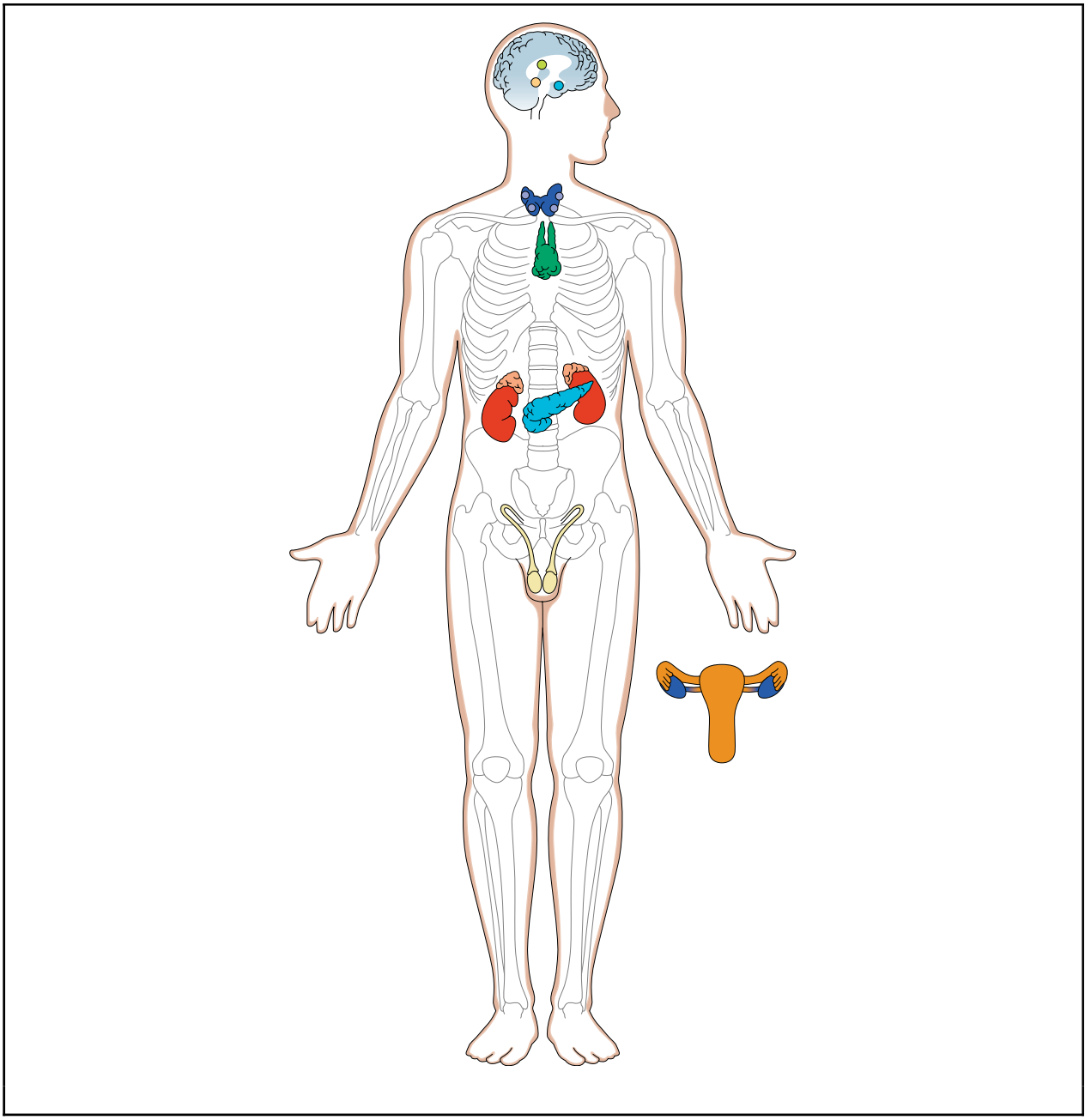
HUMAN LYMPHATIC SYSTEM. The lymphatic system and lymph nodes are shown here in pale green, the thymus in deep blue, and one of the bones rich in bone marrow (the femur) is shown here in purple. Some cancers of the lymphatic system are: Burkitt's lymphoma; Cutaneous T-cell lymphoma; Hodgkin's disease; MALT lymphoma; Mantle cell lymphoma; Sézary syndrome; and Waldenström's macroglobulinemia. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*



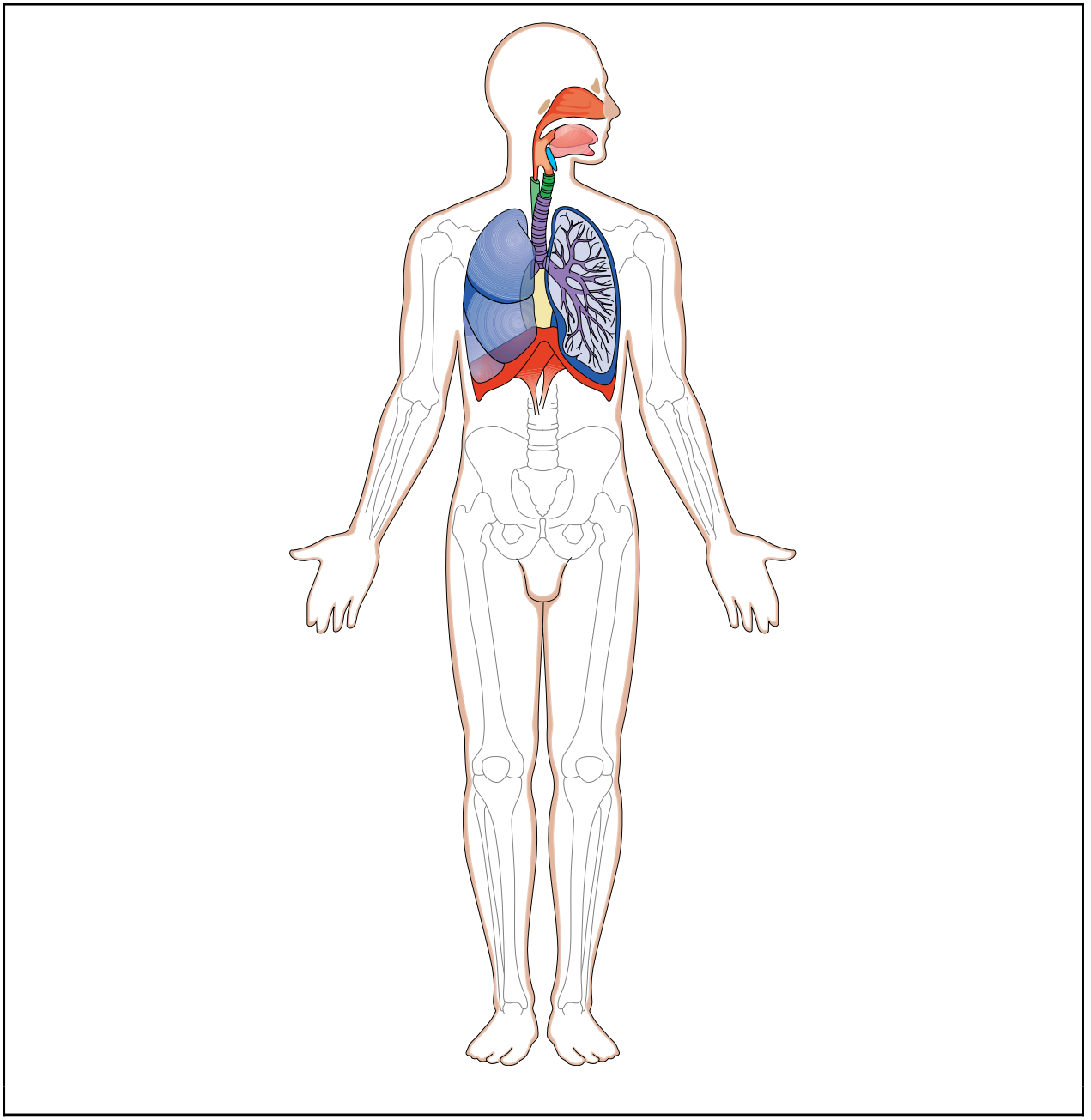
HUMAN DIGESTIVE SYSTEM. Organs and cancers of the digestive system include: Salivary glands (shown in turquoise): Salivary gland tumors. Esophagus (shown in bright yellow): Esophageal cancer. Liver (shown in bright red): Bile duct cancer; Liver cancer. Stomach (pale gray-blue): Stomach cancer. Gallbladder (bright orange against the red liver): Gallbladder cancer. Colon (green): Colon cancer. Small intestine (purple): Small intestinal cancer; can have malignant tumors associated with Zollinger-Ellison syndrome. Rectum (shown in pink, continuing the colon): Rectal cancer. Anus (dark blue): Anal cancer. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*



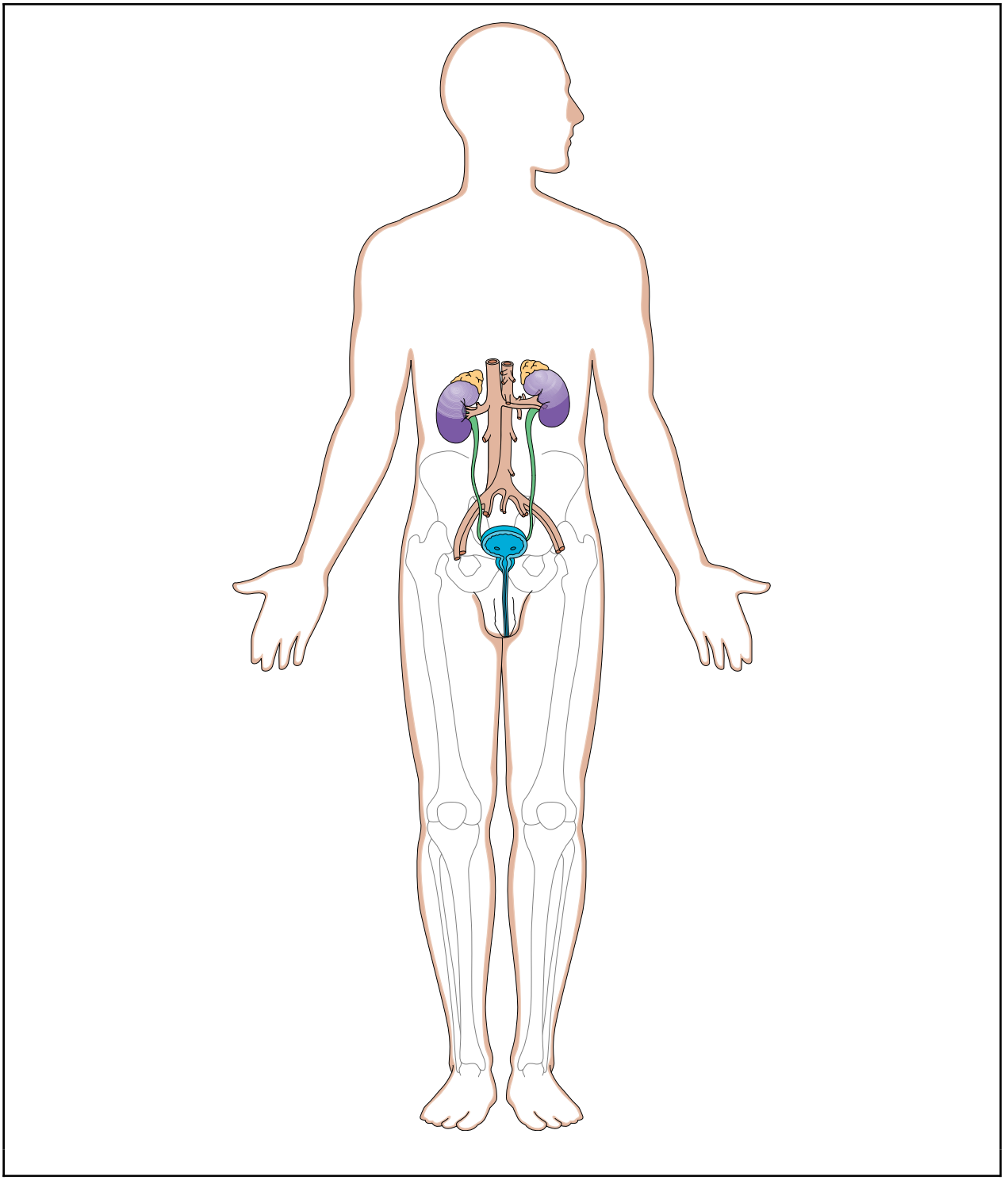
HEAD AND NECK. The pharynx, the passage that leads from the nostrils down through the neck is shown in orange. This passage is broken into several divisions. The area posterior to (behind) the nose is the nasopharynx. The area posterior to the mouth is the oropharynx. The oropharynx leads into the laryngopharynx, which opens into the esophagus (still in orange) and the larynx (shown in the large image in medium blue). Each of these regions may be affected by cancer, and the cancers include: Nasopharyngeal cancer; Oropharyngeal cancer; Esophageal cancer; and Laryngeal cancer. Oral cancers can affect the lips, gums, and tongue (pink). Referring to the smaller, inset picture of the salivary glands, salivary gland tumors can affect the parotid glands (shown here in yellow), the submandibular glands (inset picture, turquoise), and the sublingual glands (purple). *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*



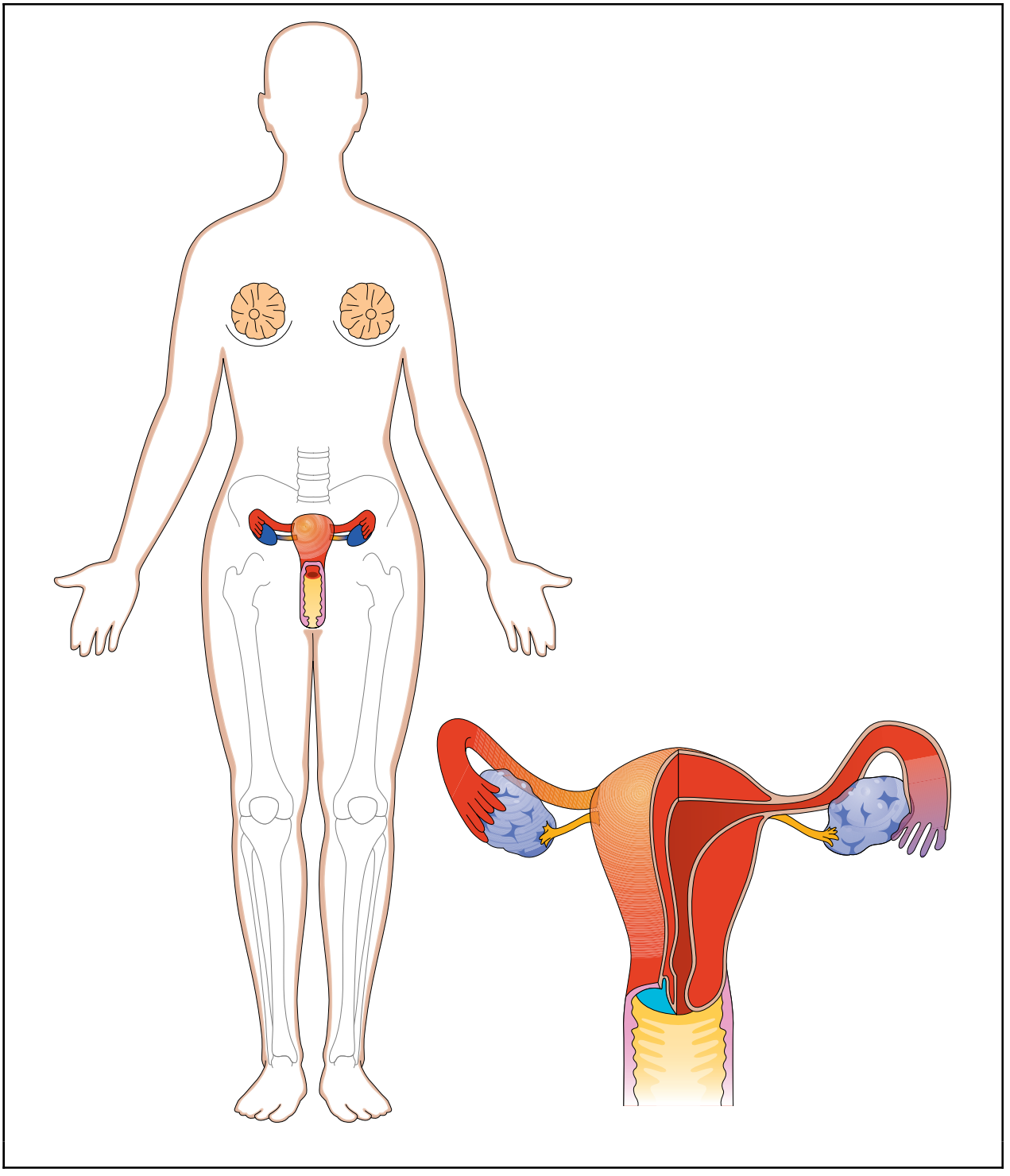
HUMAN ENDOCRINE SYSTEM. The glands and cancers of the endocrine system include: In the brain: the pituitary gland shown in blue (pituitary tumors), the hypothalamus in pale green, and the pineal gland in bright yellow. Throughout the rest of the body: Thyroid (shown in dark blue): Thyroid cancer. Parathyroid glands, four of them adjacent to the thyroid: Parathyroid cancer. Thymus (green): Thymic cancer; Thymoma. Pancreas (turquoise): Pancreatic cancer, endocrine; Pancreatic cancer, exocrine; Zollinger-Ellison syndrome tumors can be malignant and can be found in the pancreas. Adrenal glands (shown in apricot, above the kidneys): Neuroblastoma often originates in these glands; Pheochromocytoma tumors are often found in adrenal glands. Testes (in males, shown in yellow): Testicular cancer. Ovaries (in females, shown in dark blue in inset image): Ovarian cancer. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*



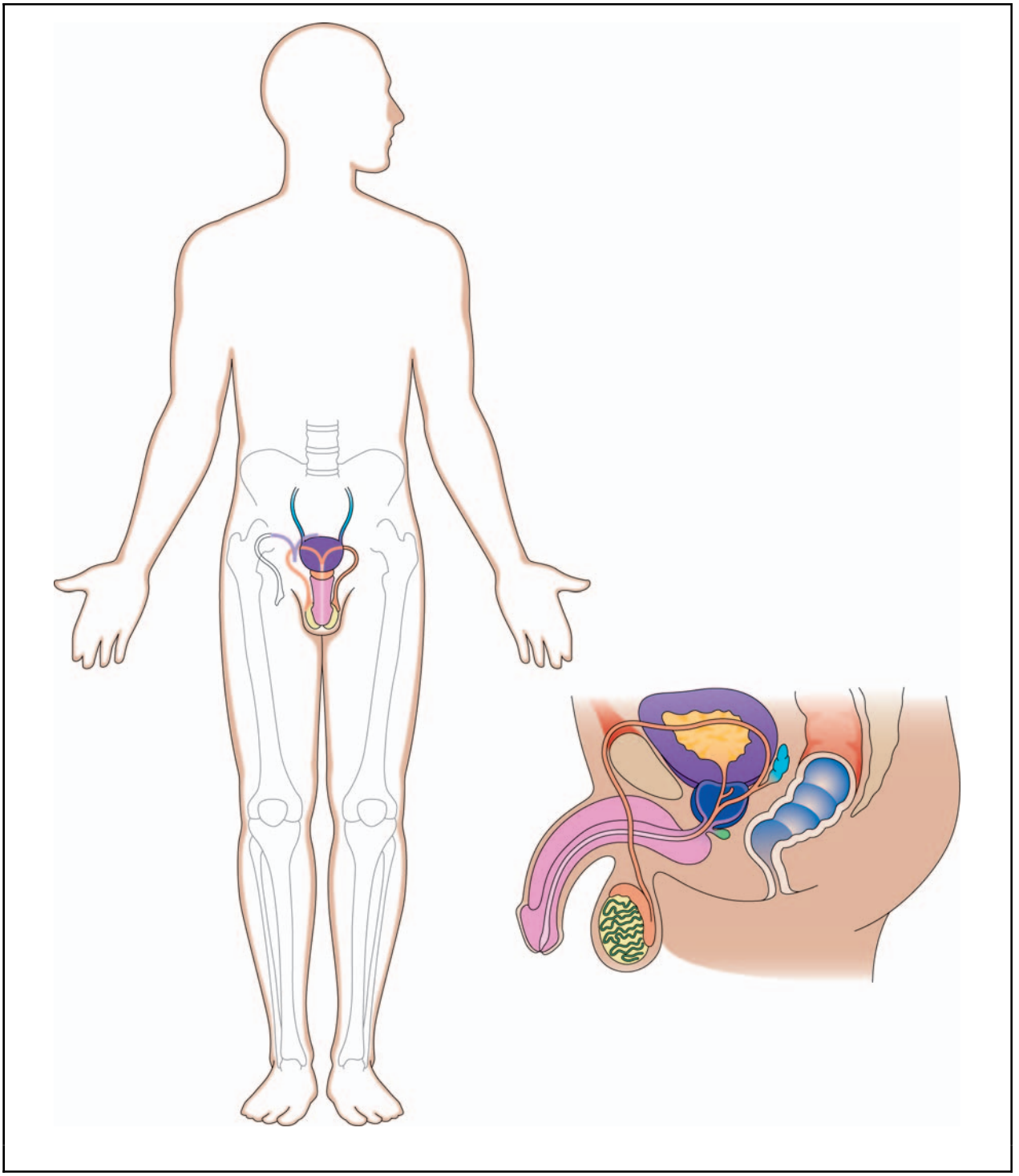
HUMAN RESPIRATORY SYSTEM. Air is breathed in through nose or mouth, enters the pharynx, shown here in orange, and passes through the larynx, shown here as a green tube with a ridged texture. (The smooth green tube shown is the esophagus, which is posterior to the larynx and which is involved in digestion instead of breathing.) The air then passes into the trachea (purple), a tube that divides into two tubes called bronchi. One bronchus passes into each lung, and continues to branch within the lung. These branches are called bronchioles and each bronchiole leads to a tiny cluster of air sacs called alveoli, where the exchange of gases occurs, so that the air and gases breathed in get diffused to the blood. The lungs (deep blue) are spongy and have lobes and can be affected by Lung cancer, both the non-small cell and small-cell types. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*



HUMAN URINARY SYSTEM. Organs and cancers of the urinary system include: Kidneys (shown in purple): Kidney cancer; Renal pelvis tumors; Wilms' tumor. Ureters are shown in green. Bladder (blue-green): Bladder cancer. The kidneys, bladder, or ureters can be affected by a cancer type called Transitional cell carcinoma. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*



FEMALE REPRODUCTIVE SYSTEM. Organs and cancers of the female reproductive system include: Uterus, shown in red with the uterine or Fallopian tubes: Endometrial cancer. Ovaries (blue): Ovarian cancer. Vagina (shown in pink with a yellow interior or lining): Vaginal cancer. Breasts: Breast cancer; Paget's disease of the breast. Shown in detailed inset only in turquoise, Cervix: Cervical cancer. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*



MALE REPRODCTIVE SYSTEM. Organs, glands, and cancers of the male reproductive system include: Penis (shown in pink): Penile cancer. Testes (shown in yellow): Testicular cancer. Prostate gland (shown in full-body illustration in a peach/ apricot color, and in the inset as the dark blue gland between the bladder and the penis): Prostate cancer. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*

A

2-CdA *see* **Cladribine**

5-Azacitidine *see* **Azacitidine**

5-Fluorouracil *see* **Fluorouracil**

6-Mercaptopurine *see* **Mercaptopurine**

6-Thioguanine *see* **Thioguanine**

Abarelix

Definition

Abarelix is an injectable gonadotrophin-releasing hormone (GnRH) antagonist that is used to decrease the production of the male hormone **testosterone**.

Purpose

Abarelix is used in men to treat advanced **prostate cancer** that has not responded to other treatments or when other treatments have been refused. The prostate gland lies under the bladder and surrounds the urethra. Its main function is to produce seminal fluid that mixes with sperm prior to ejaculation. Prostate cancer is the most common cancer in men over the age of 50.

Other treatments for prostate cancer should be tried before treatment with abarelix is prescribed. Early stage prostate cancer is often treated with surgery or **radiation therapy** and less often with **cryoablation**. Advanced stage prostate cancer may be treated with other drugs that decrease the production of testosterone. Another approach to treating advanced prostate cancer is surgical removal of the testicles (castration). Some men reject this surgery, making them candidates for treatment with abarelix.

Because abarelix can cause serious side effects, this drug is considered appropriate for use only in the following situations:

- The cancer has spread (metastasized) and is close to the spinal column, so that there is a risk that pressure will cause damage to the spinal nerves.
- The urethra or bladder is blocked because of malignant tissue growth making urination difficult or impossible.
- Prostate cancer causes severe pain in the bones that narcotic pain medication cannot control.

Description

Abarelix works by blocking gonadotropin-releasing hormone (GRH) a hormone released from the anterior pituitary gland that stimulates the production of testosterone. When this messenger hormone from the pituitary is blocked, the level of testosterone in the blood decreases. Prostate cancer cells grow best in the presence of testosterone, so by decreasing the amount available, growth of the tumor is slowed or stopped. Other drugs (**leuprolide acetate** [Lupron], **goserelin acetate** [Zoladex]) are available that also decrease testosterone production. One advantage of abarelix over these other drugs is that the other drugs used to decrease testosterone levels first stimulate the production of testosterone then decrease it. With abarelix, there is no initial increase in testosterone production and decline in production of the hormone begins immediately. However, abarelix may stop working in some men after an initial period of effectiveness. The drug does not cure prostate cancer but can relieve symptoms.

Abarelix is manufactured in the United States by Praecis Pharmaceuticals and sold under the brand name Plenaxis. Generic substitutes are not available, and as of 2005 there is only one American manufacturer. Abarelix was approved for use by the United States Food and Drug Administration (FDA) in December 2003 with restrictions. The drug can only be administered by doctors who are registered in the Plenaxis PLUS Program (Plenaxis User Safety Program) because of its potentially life-threatening side effects.

Recommended dosage

Abarelix is an injectable liquid. It is supplied as powder in single dose vial to which the physician adds a small amount of saline (saltwater) before use. The resulting liquid is injected into the buttocks muscle. The treatment cycle calls for an initial injection on days 1, 15, and 29 followed by an injection every 28 days. The testosterone level of the blood should be checked after the first month and then about every eight weeks to assure that the drug is continuing to work. Liver function tests should also be done regularly, as abarelix may cause changes in the liver function. These changes are usually not permanent and go away once the drug is stopped.

Precautions

Certain individuals should not use abarelix. These include women, children under age 18, and men with a rare heart condition called prolongation of the QTc interval. Men with osteoporosis, liver disease, and blood clotting disorders should identify these existing problems to their doctor before beginning treatment. Abarelix may stop working in some men and is more likely to stop working in men weighing over 225 lb (102 kg). There are no special dietary restriction when receiving abarelix therapy.

Side effects

Abarelix can cause serious or life-threatening allergic reactions either during or after administration. Therefore, the drug can only be administered by a physician registered in the Plenaxis PLUS safety program. The likelihood of life-threatening reactions increases with each injection of abarelix. For this reason, men receiving an injection of abarelix must remain under observation in the doctor's office for at least 30 minutes following each treatment.

Symptoms of rare but life-threatening reactions include:

- low blood pressure, fainting, shock
- swelling of the face, eyelids, tongue, or throat
- wheezing, asthma, tightness in the chest, difficulty breathing

More common but less serious side effects include:

- hot flashes
- rapid heart beat (tachycardia)
- rash, hives, **itching**, skin redness
- vomiting
- jaundice (yellowing of the whites of the eyes or skin)
- stomach pain
- breast enlargement
- problems sleeping
- breast, back or other pain
- constipation
- changes in the electrical profile of the heart

KEY TERMS

Antagonist—A drug or chemical that works against or blocks another chemical.

Cryoablation—The selective freezing of cancerous tissue in order to kill it.

Osteoporosis—A condition in which mineral is dissolved out of bone and bones become weakened and easily broken.

Pituitary gland—A tissue located at the base of the brain that is divided into two parts (anterior and posterior). The pituitary gland produces many different hormones that regulate body metabolism or control the production of other hormones.

Testes—Male reproductive organs that produce sperm and the hormone testosterone.

Urethra—The tube that drains urine from the bladder.

Interactions

It is important for patients to discuss with their physician all prescription medications, over-the-counter medications, and herbal or alternative remedies that the patients are taking before treatment with abarelix is begun. Although as of 2005 formal drug interaction studies have not been completed, a number of drugs may interact with abarelix. These include:

- arsenic trioxide
- astemizole (Hismanal)
- bepridil (Vascor)
- certain antibiotics
- cisapride (Propulsid)
- cyclobenzaprine (Flexeril)
- DHEA (dietary supplement)
- dolasetron (Anzemet)
- droperidol
- halofantrine (Halfan)
- estrogen or other female hormones
- levomethadyl (Orlaam)
- medications that regulate heart rhythm

- medications that treat depression
- palonosetron (Aloxi)
- pentamidine (Pentam)
- phenothiazines (found in antihistamines)
- pimozide (Orap)
- probucol (Lorelco)

Tish Davidson, A. M.

Accelerated partial breast irradiation

Definition

Accelerated partial breast irradiation (APBI), also referred to as high dose rate breast brachytherapy, is a shortened course of high dose **radiation therapy** that is given to **breast cancer** patients and targets the area of the breast where the cancer is most likely to recur.

Purpose

One of the purposes of APBI is to reduce the radiation treatment time from seven or eight weeks, which is generally required with conventional whole breast irradiation, to four or five days. Planning for seven or eight weeks of radiation treatment is difficult for many women, especially women who work outside the home, are single parents, and/or live in rural areas. Reducing the treatment time to one week is not only more convenient for many patients, but it also helps them with emotional closure. In other words, the sooner they are done with the treatments, the sooner they can put the cancer behind them.

Another purpose of APBI is to save the breast while still preventing a recurrence of the cancer. In fact, Robert R. Kuske, M.D., a radiation oncologist who has led several **clinical trials** investigating high dose rate breast brachytherapy, is quick to point out that nearly "80% of women diagnosed with breast cancer are candidates for breast conservation therapy, in which the lump is surgically removed and any remaining cancerous cells are destroyed by radiation therapy, leaving the breast intact." Nonetheless, nearly 45% of the women that qualify for breast conservation therapy choose to have a **mastectomy** anyway, despite the fact that twenty years of research validates that there is no difference in the survival rates of women that choose to have a mastectomy rather than a **lumpectomy** followed by radiation therapy. Dr. Kuske believes that the patients who could choose to save their breasts opt for a mastectomy because they are not only unable to face the inconvenience of many weeks of external beam radiation therapy, but they also fear the effects of whole breast irradiation on their uninvolved breast, skin, ribs, lung, and heart. Therefore, patients with these concerns may find APBI a more favorable option, given that the treatment time is shorter and, due to the way the treatment is delivered, "less radiation will reach the skin, lungs, heart, ribs, the healthy part of the breast, and the body as a whole," as explained by the Cancer Treatment Centers of America.

KEY TERMS

External beam radiation therapy—Sometimes referred to as whole breast irradiation, external beam radiation therapy is delivered by a machine that is placed outside the body and is aimed to deliver radiation at the cancer site. Technically, as many experts have pointed out, the machine doesn't deliver radiation to the entire breast; however, sometimes the surrounding normal tissues are affected.

A wealth of cancer specialists recommend that a certain criteria be considered when breast cancer patients are selected for APBI rather than whole breast irradiation. It is generally agreed that the patient should be older than forty-five years of age; the American Society of Breast Surgeons prefers, in fact, that the patient be older than fifty years of age. The extent of lymph node involvement must be considered and the patient should have "negative microscopic surgical margins of at least 2 mm in all directions," according to the American Society of Breast Surgeons. Opinions vary regarding tumor size. For example, the experts at the Cancer Treatment Centers of America believe that the tumor should be 4 cm or less in size. Others, such as the American Society of Breast Surgeons, take a more conservative view and believe that only patients with tumors 2 cm or less should be considered for the treatment.

Description

High Dose Rate Breast Brachytherapy

There are two ways to accomplish the administration of APBI, both of which can be done on an outpatient basis. One way, called high does rate breast brachytherapy, involves inserting multiple plastic tubes, referred to as catheters, in the breast area surrounding

QUESTIONS TO ASK YOUR DOCTOR

- How often have you performed this procedure?
- How painful is it to have the catheters inserted and removed?
- What do I need to do to avoid infection?
- Can I expect any numbness or nerve damage from the treatment?
- Do many of your patients express regret over choosing APBI over external beam radiation therapy?

the lumpectomy cavity. A tiny radioactive seed, which delivers the correct amount of radiation, is inserted in the catheters. Generally, the treatment is given twice a day for five days, although some treatment regimes vary according to the individual needs of the patient. Treatment sessions usually take no longer than 20 minutes. At the end of the five-day treatment, the catheters are removed.

Some patients experience minor discomfort due to the insertion and removal of the catheters, whereas others do not. Because the treatment is more invasive than external beam radiation therapy, patients should talk with their physicians regarding what pain, if any, they might experience. For the most part, however, patients are able to return to their daily routine after each treatment.

Mammosite Breast Brachytherapy

Another way to administer APBI is called mammosite breast brachytherapy, which is also known as balloon catheter brachytherapy. In this case, a small balloon is attached to a single catheter, which is inserted into the lumpectomy cavity. Then the balloon is inflated and a computer-controlled machine places the high dose radioactive seed inside the balloon. The experts at the Cancer Treatment Centers of America point out that, "some women interested in this treatment are finding out that they do not qualify because of breast shape or because they so not have a fluid filled cavity remaining in their breast after a lumpectomy." Fortunately, this does not disqualify them from the other method of administering APBI.

The radioactive seeds are removed after each appointment; therefore, patients will not be rendered radioactive between their appointments or after their final appointment. Both types of brachytherapy are covered under most insurance plans.

Aftercare

Many patients report redness, bruising, and breast pain, such as soreness. Some minor scarring can be expected as well.

Risks

As with any surgical procedure, there are risks. Patients should talk to their doctors regarding their individual risk factors.

Treatment Outcomes

More clinical studies need to be conducted to support the data currently available regarding APBI treatment outcomes. Until that time, Douglas Arthur, M.D., suggests that "it appears appropriate for those offering APBI to adhere to the conservative principles outlined in the reports available from the American Brachytherapy Society and the American Society of Breast Surgeons."

Resources

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Lee Ann Paradise

Acoustic neuroma

Definition

An acoustic neuroma is a benign tumor involving cells of the myelin sheath that surrounds the vestibulocochlear nerve (eighth cranial nerve).

Description

The vestibulocochlear nerve extends from the inner ear to the brain and is made up of a vestibular branch, often called the vestibular nerve, and a cochlear branch, called the cochlear nerve. The vestibular and cochlear nerves lie next to one another. They also run along side other cranial nerves. People possess two of each type of vestibulocochlear nerve, one that extends from the left ear and one that extends from the right ear.

The vestibular nerve transmits information concerning balance from the inner ear to the brain and the cochlear nerve transmits information about hearing. The vestibular nerve, like many nerves, is surrounded by a cover called a myelin sheath. A tumor called a schwannoma can sometimes develop from the cells of the myelin sheath. A tumor is an abnormal growth of tissue that results from the uncontrolled growth of cells. Acoustic neuromas are often called vestibular schwannomas because they are tumors that arise from the myelin sheath that surrounds the vestibular nerve. Acoustic neuromas are considered benign (non-cancerous) tumors since they do not spread to other parts of the body. They can occur anywhere along the vestibular nerve but are most likely to occur where the vestibulocochlear nerve passes through the tiny bony canal that connects the brain and the inner ear.

An acoustic neuroma can arise from the left vestibular nerve or the right vestibular nerve. A unilateral tumor is a tumor arising from one nerve and a bilateral tumor arises from both vestibular nerves. Unilateral acoustic neuromas usually occur spontaneously (by chance). Bilateral acoustic neuromas occur as part of a hereditary condition called Neurofibromatosis Type 2 (NF2). A person with NF2 has inherited a predisposition for developing acoustic neuromas and other tumors of the nerve cells.

Acoustic neuromas usually grow slowly and can take years to develop. Some acoustic neuromas remain so small that they do not cause any symptoms. As the acoustic neuroma grows, it can interfere with the functioning of the vestibular nerve and can cause vertigo and balance difficulties. If the acoustic nerve grows large enough to press against the cochlear nerve, then hearing loss and a ringing (tinnitus) in the affected ear will usually occur. If untreated and the acoustic neuroma continues to grow, it can press against other nerves in the region and cause other symptoms. This tumor can be life threatening if it becomes large enough to press against and interfere with the functioning of the brain.

Causes and symptoms

Causes

An acoustic neuroma is caused by a change or absence of both of the NF2 tumor suppressor genes in a nerve cell. Every person possesses a pair of NF2 genes in every cell of their body including their nerve cells. One NF2 gene is inherited from the egg cell of the mother and one NF2 gene is inherited from the sperm cell of the father. The NF2 gene is responsible for helping to prevent the formation of tumors in the nerve cells. In particular the NF2 gene helps to prevent acoustic neuromas.

Only one unchanged and functioning NF2 gene is necessary to prevent the formation of an acoustic neuroma. If both NF2 genes become changed or missing in one of the myelin sheath cells of the vestibular nerve, then an acoustic neuroma will usually develop. Most unilateral acoustic neuromas result when the NF2 genes become spontaneously changed or missing. Someone with a unilateral acoustic neuroma that has developed spontaneously is not at increased risk for having children with an acoustic neuroma. Some unilateral acoustic neuromas result from the hereditary condition NF2. It is also possible that some unilateral acoustic neuromas may be caused by changes in other genes responsible for preventing the formation of tumors.

Bilateral acoustic neuromas result when someone is affected with the hereditary condition NF2. A person with NF2 is typically born with one unchanged and one changed or missing NF2 gene in every cell of their body. Sometimes they inherit this change from their mother or father. Sometimes the change occurs spontaneously when the egg and sperm come together to form the first cell of the baby. The children of a person with NF2 have

a 50% chance of inheriting the changed or missing NF2 gene.

A person with NF2 will develop an acoustic neuroma if the remaining unchanged NF2 gene becomes spontaneously changed or missing in one of the myelin sheath cells of their vestibular nerve. People with NF2 often develop acoustic neuromas at a younger age. The mean age of onset of acoustic neuroma in NF2 is 31 years of age versus 50 years of age for sporadic acoustic neuromas. Not all people with NF2, however, develop acoustic neuromas. People with NF2 are at increased risk for developing cataracts and tumors in other nerve cells.

Most people with a unilateral acoustic neuroma are not affected with NF2. Some people with NF2, however, only develop a tumor in one of the vestibulocochlear nerves. Others may initially be diagnosed with a unilateral tumor but may develop a tumor in the other nerve a number of years later. NF2 should be considered in someone under the age of 40 who has a unilateral acoustic neuroma. Someone with a unilateral acoustic neuroma and other family members diagnosed with NF2 probably is affected with NF2. Someone with a unilateral acoustic neuroma and other symptoms of NF2 such as cataracts and other tumors may also be affected with NF2. On the other hand, someone over the age of 50 with a unilateral acoustic neuroma, no other tumors and no family history of NF2 is very unlikely to be affected with NF2.

Recent studies in Europe have suggested a possible connection between the widespread use of mobile phones and an increased risk of developing acoustic neuromas. Some observers, however, question whether mobile phones have been in use long enough to be an identifiable risk factor.

Symptoms

Small acoustic neuromas usually only interfere with the functioning of the vestibulocochlear nerve. The most common first symptom of an acoustic neuroma is hearing loss, which is often accompanied by a ringing sound (tinnitis). People with acoustic neuromas sometimes report difficulties in using the phone and difficulties in perceiving the tone of a musical instrument or sound even when their hearing appears to be otherwise normal. In most cases the hearing loss is initially subtle and worsens gradually over time until deafness occurs in the affected ear. In approximately 10% of cases the hearing loss is sudden and severe.

Acoustic neuromas can also affect the functioning of the vestibular branch of the vestibulocochlear nerve and van cause vertigo and dysequilibrium. Twenty percent of small tumors are associated with periodic vertigo, which is characterized by dizziness or a whirling sensation. Larger acoustic neuromas are less likely to cause vertigo but more likely to cause dysequilibrium. Dysequilibrium, which is characterized by minor clumsiness and a general feeling of instability, occurs in nearly 50% of people with an acoustic neuroma.

As the tumor grows larger, it can press on the surrounding cranial nerves. Compression of the fifth cranial nerve can result in facial pain and or numbness. Compression of the seventh cranial nerve can cause spasms, weakness or paralysis of the facial muscles. Double vision is a rare symptom but can result when the sixth cranial nerve is affected. Swallowing and/or speaking difficulties can occur if the tumor presses against the ninth, tenth, or twelfth cranial nerves.

If left untreated, the tumor can become large enough to press against and affect the functioning of the brain stem. The brain stem is the stalk-like portion of the brain that joins the spinal cord to the cerebrum, the thinking and reasoning part of the brain. Different parts of the brainstem have different functions such as the control of breathing and muscle coordination. Large tumors that impact the brain stem can result in headaches, walking difficulties (gait ataxia) and involuntary shaking movements of the muscles (tremors). In rare cases when an acoustic neuroma remains undiagnosed and untreated it can cause nausea, vomiting, lethargy and eventually coma, respiratory difficulties and death. In the vast majority of cases, however, the tumor is discovered and treated long before it is large enough to cause such serious manifestations.

Diagnosis

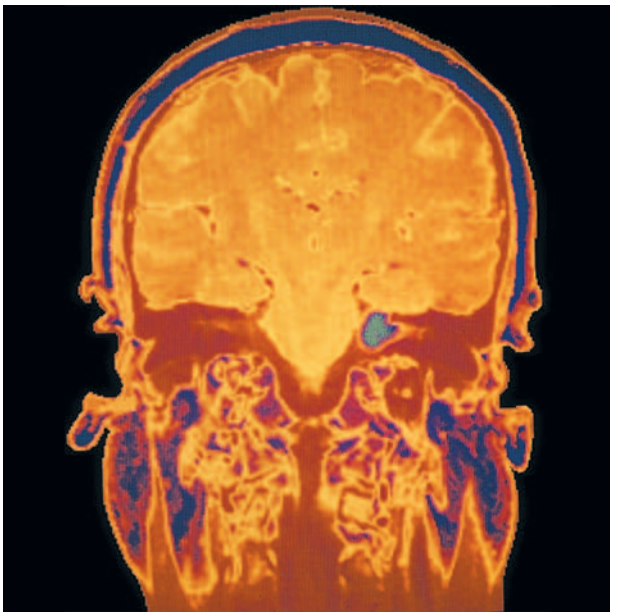
Anyone with symptoms of hearing loss should undergo hearing evaluations. Pure tone and speech audiometry are two screening tests that are often used to evaluate hearing. Pure tone audiometry tests to see how well someone can hear tones of different volume and pitch and speech audiometry tests to see how well someone can hear and recognize speech. An acoustic neuroma is suspected in someone with unilateral hearing loss or hearing loss that is less severe in one ear than the other ear(asymmetrical).

Sometimes an auditory brainstem response (ABR, BAER) test is performed to help establish whether someone is likely to have an acoustic neuroma. During the ABR examination, a harmless electrical impulse is passed from the inner ear to the brainstem. An acoustic neuroma can interfere with the passage of this electrical impulse and this interference can, sometimes be identified through the ABR evaluation. A normal ABR examination does

not rule out the possibility of an acoustic neuroma. An abnormal ABR examination increases the likelihood that an acoustic neuroma is present but other tests are necessary to confirm the presence of a tumor.

If an acoustic neuroma is strongly suspected then **magnetic resonance imaging** (MRI) is usually performed. The MRI is a very accurate evaluation that is able to detect nearly 100% of acoustic neuromas. **Computed tomography** (CT scan, CAT scan) is unable to identify smaller tumors; but it can be used when an acoustic neuroma is suspected and an MRI evaluation cannot be performed.

Once an acoustic neuroma is diagnosed, an evaluation by genetic specialists such as a geneticist and genetic counselor may be recommended. The purpose of this evaluation is to obtain a detailed family history and check for signs of NF2. If NF2 is strongly suspected then DNA testing may be recommended. DNA testing involves checking the blood cells obtained from a routine blood draw for the common gene changes associated with NF2.



False-color magnetic resonance image (MRI) scan of a coronal section of the head & brain of someone suffering from an acoustic neuroma (green circular area). *(Photograph by Mehau Kulyk, Photo Researchers, Inc. Reproduced by permission.)*

Treatment

The three treatment options for acoustic neuroma are surgery, radiation, and observation. The physician and patient should discuss the pros and cons of the different options prior to making a decision about treatment. The patient's physical health, age, symptoms, tumor size, and tumor location should be considered.

Microsurgery

The surgical removal of the tumor or tumors is the most common treatment for acoustic neuroma. In most cases the entire tumor is removed during the surgery. If the tumor is large and causing significant symptoms, yet there is a need to preserve hearing in that ear, then only part of the tumor may be removed. During the procedure the tumor is removed under microscopic guidance and general anesthetic. Monitoring of the neighboring cranial nerves is done during the procedure so that damage to these nerves can be prevented. If preservation of hearing is a possibility, then monitoring of hearing will also take place during the surgery.

Most people stay in the hospital four to seven days following the surgery. Total recovery usually takes four to six weeks. Most people experience **fatigue** and head discomfort following the surgery. Problems with balance and head and neck stiffness are also common. The mortality rate of this type of surgery is less than 2% at most major centers. Approximately 20% of patients experience some degree of post-surgical complications. In most cases these complications can be managed successfully and do not result in long term medical problems. Surgery brings with it a risk of stroke, damage to the brain stem, infection, leakage of spinal fluid and damage to the cranial nerves. Hearing loss and/or tinnitis often result from the surgery. A follow-up MRI is recommended one to five years following the surgery because of possible regrowth of the tumor.

Stereotactic radiation therapy

During stereotactic **radiation therapy**, also called radiosurgery or radiotherapy, many small beams of radiation are aimed directly at the acoustic neuroma. The radiation is administered in a single large dose, under local anesthetic and is performed on an outpatient basis. This results in a high dose of radiation to the tumor but little radiation exposure to the surrounding area. This treatment approach is limited to small or medium tumors. The goal of the therapy is to cause tumor shrinkage or at least limit the growth of the tumor. The long-term efficacy and risks of this treatment approach are not known; however, as of the early 2000s, more and more patients with acoustic neuromas are choosing this approach over conventional surgery. Periodic MRI monitoring throughout the life of the patient is therefore recommended.

KEY TERMS

Benign tumor—A localized overgrowth of cells that does not spread to other parts of the body.

Chromosome—A microscopic structure, made of a complex of proteins and DNA, that is found within each cell of the body.

Cranial nerves—The set of twelve nerves found on each side of the head and neck that control the sensory and muscle functions of a number of organs such as the eyes, nose, tongue face and throat.

Computed tomography (CT)—An examination that uses a computer to compile and analyze the images produced by x rays projected at a particular part of the body.

DNA testing—Testing for a change or changes in a gene or genes.

Gene—A building block of inheritance, made up of a compound called DNA (deoxyribonucleic acid) and containing the instructions for the production of a particular protein. Each gene is found on a specific location on a chromosome.

Magnetic resonance imaging (MRI)—A test which uses an external magnetic field instead of x rays to visualize different tissues of the body.

Myelin sheath—The cover that surrounds many nerve cells and helps to increase the speed by which information travels along the nerve.

Neurofibromatosis type 2 (NF2)—A hereditary condition associated with an increased risk of bilateral acoustic neuromas, other nerve cell tumors and cataracts.

Protein—A substance produced by a gene that is involved in creating the traits of the human body such as hair and eye color or is involved in controlling the basic functions of the human body.

Schwannoma—A tumor derived from the cells of the myelin sheath that surrounds many nerve cells.

Tinnitus—A ringing sound or other noise in the ear.

Vertigo—A feeling of spinning or whirling.

Vestibulocochlear nerve (Eighth cranial nerve)—Nerve that transmits information, about hearing and balance from the ear to the brain.

Radiation therapy can cause hearing loss which can sometimes occurs even years later. Radiation therapy can also cause damage to neighboring cranial nerves, which can result in symptoms such as numbness, pain or paralysis of the facial muscles. In many cases these symptoms are temporary. Radiation treatment can also induce the formation of other benign or malignant schwannomas. This type of treatment may therefore be contraindicated in the treatment of acoustic neuromas in those with NF2 who are predisposed to developing schwannomas and other tumors.

Observation

Acoustic neuromas are usually slow-growing; in some cases they will stop growing and even become smaller or disappear entirely. It may therefore be appropriate in some cases to hold off on treatment and to periodically monitor the tumor through MRI evaluations. Long-term observation may be appropriate for example in an elderly person with a small acoustic neuroma and few symptoms. Periodic observation may also be indicated for someone with a small and asymptomatic acoustic neuroma that was detected through an evaluation for another medical problem. Observation may also be suggested for someone with an acoustic neuroma in the only hearing ear or in the ear that has better hearing. The danger of an observational approach is that as the tumor grows larger it can become more difficult to treat.

Prognosis

The prognosis for someone with a unilateral acoustic neuroma is usually quite good provided the tumor is diagnosed early and appropriate treatment is instituted. Long-term hearing loss and tinnitis in the affected ear are common, even if appropriate treatment is provided. Many patients also experience facial weakness, balance problems, and headaches. Regrowth of the tumor is also a possibility following surgery or radiation therapy and repeat treatment may be necessary. The prognosis can be poorer for those with NF2 who have an increased risk of bilateral acoustic neuromas and other tumors.

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Lisa Andres, M.S., CGC
Rebecca J. Frey, PhD

Acquired Immune Deficiency syndrome *see* **AIDS-related cancers**

Actinomycin D *see* **Dactinomycin**

Acute erythroblastic leukemia

Definition

Acute erythroblastic leukemia, also called erythremic myelosis, DiGuglielmo syndrome, or erythroleukemia, results from uncontrolled proliferation of immature erythrocytes (red blood cells).

Description

Acute erythroblastic leukemia, a variant of **acute myelocytic leukemia**, originates in the blood and in the bone marrow. In this form of leukemia, a large number of abnormal, immature red blood cells are produced. The advanced phase is also called the blast crisis. At this stage, over 50% of the cells in the bone marrow are immature malignant cells (also called blast cells or promelocytes).

Demographics

There are no statistics available for this rare form of cancer.

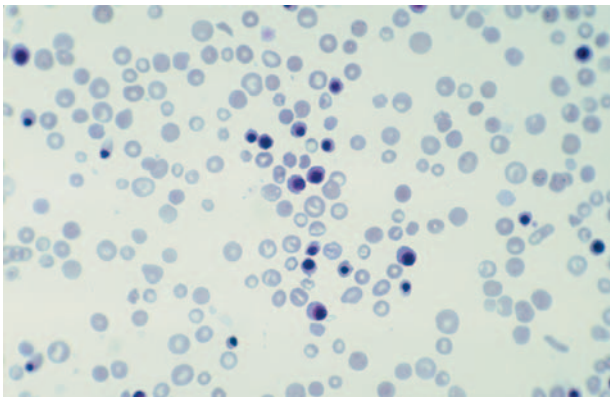
Causes and symptoms

The causes of acute erythroblastic leukemia are largely unknown. However, acute erythroblastic leukemia constitutes 10–20% of leukemias secondary to radiation, alkylator therapy, or overexposure to benzene.

Patients with this type of leukemia have less than the normal amount of healthy red blood cells and platelets, which results in insufficient amounts of oxygen being carried through the body. This condition is called **anemia**, and causes patients to experience severe weakness and tiredness. Patients may have less than the normal number of white blood cells as well. Other symptoms include **fever**, chills, loss of appetite and weight, easy bleeding or bruising (due to lower than normal platelet levels), bone or joint pain, headaches, vomiting, and confusion. In addition, patients with leukemia may have hepatosplenomegaly, an enlargement of the liver and spleen. Enlargement of these organs is noticed as a fullness or swelling in the abdomen, and can be felt by a doctor during a physical examination. The occurrence of Sweet's syndrome, a rare skin disorder accompanied by fever, inflammation of the joints (arthritis), and the sudden onset of a rash, has also been associated with acute erythroblastic leukemia.

Diagnosis

Patients seeking treatment usually report a vague history of chronic general **fatigue**. Blood tests are used to



Erythroblastic leukemia cells. *(Copyright Richard Green, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

establish the diagnosis. A sample of blood is examined under a microscope to identify abnormal red cells—which are larger than healthy cells—and to count the number of mature cells and blasts present. Cancer red cell precursors predominate, myeloid blasts also are seen, and multinucleated red cell precursors are common. Bone marrow examinations are also performed, either by aspiration or **biopsy** to examine the cell types further.

Treatment

Treatment for acute erythroblastic leukemia depends on the features of the cancer cells present and on the extent of the disease, as well as on the age of the patient, his symptoms, and general health condition. This disease can have an indolent course and may only require observation in the early stages. The treatment strategy is based on **chemotherapy** and in some patients, bone marrow or cell transplantations are indicated as well. Chemotherapy is usually administered in combinations of two or more drugs. Post-remission therapy includes maintenance chemotherapy for most patients.

Clinical staging, treatments, and prognosis

Acute erythroblastic leukemia is a very aggressive form of leukemia and does not respond well to the types of therapy used for a related type of cancer known as **acute myelocytic leukemia**. However, recent advances in chemotherapy protocols and **bone marrow transplantation** techniques, either allogeneic or autologous, have been identified as a means to increase the cure rate. The patient's cancerous bone marrow is first purged using drugs and **radiation therapy** before being replaced by healthy bone marrow that is obtained from a suitable donor (allogeneic) or from the patient himself (autologous). In the case of an autologous transplant, the bone marrow is treated outside the patient's body to remove the cancer cells before transplantation.

KEY TERMS

Allogeneic bone marrow transplant—A bone marrow transplant using bone marrow obtained from a genetically matched healthy donor, such as a sister or a brother.

Autologous bone marrow transplant—A bone marrow transplant that uses the patient's own bone marrow.

Anemia—A condition in which the number of red blood cells is below normal

Blast cells—Immature cancer cells. Also called promelocytes.

Bone marrow aspiration—Common technique used to obtain a bone marrow sample from a patient. A needle is inserted into a marrow-containing bone, such as the hip (iliac crest) or sternum (breast bone) and a small amount of liquid bone marrow is removed for examination.

Bone marrow biopsy—Another common technique used to obtain a bone marrow sample from a patient. Like bone marrow aspiration, it is performed with a needle, but a larger one is used and a small piece of bone is removed as well as bone marrow.

Chemotherapy—The treatment of disease by means of chemicals. In cancer, the chemicals selectively destroy cancerous tissue. When cancer remission occurs, a course of maintenance chemotherapy is often prescribed so as to prevent recurrence.

Erythrocyte—Red blood cell.

Leukemia—Cancer of the blood-forming tissues.

Myeloid blast cell—Type of cancer cell originating in the bone marrow.

Platelet—A type of blood cell responsible for blood coagulation and for the repair of damaged blood vessels.

Proliferation—Rapid reproduction of tissue.

Remission—Complete or partial disappearance of the symptoms of cancer following treatment.

Coping with cancer treatment

Like all types of leukemias, patients with acute erythroblastic leukemia usually experience a number of

QUESTIONS TO ASK THE DOCTOR

- How can I obtain information on a rare cancer such as acute erythroblastic leukemia?
- How are my chances of recovery affected by the fact that this cancer is so rare?

specific complications and side effects resulting from treatment, as well as emotional concerns. They require supportive care to cope with these issues and to maintain their comfort and quality of life during treatment. As with every serious disease, psychological stress is increased and it is important for patients to be able to discuss their needs and concerns about tests, treatments, hospital stays, and financial consequences of the illness. Family, friends, doctors, nurses, and other members of the health care team are the best sources of support, as well as social workers, counselors, and members of the clergy.

Clinical trials

In 2005, no **clinical trials** for this leukemia were registered with the National Cancer Institute.

Prevention

Since this form of cancer is very rare and its causes are largely unknown, no specific preventive measures can be recommended.

Special concerns

Patients diagnosed with acute erythroblastic leukemia require special support in that they must deal with having a rare form of cancer about which there is very little specific information available. This creates additional anxiety and special care must be taken to explain to the patient that an uncommon cancer is not an untreatable one.

See also Bone marrow aspiration and biopsy; Chronic myelocytic leukemia; Myeloproliferative diseases.

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Monique Laberge, PhD

Acute leukemia

Definition

A rapidly progressing cancer that starts in the blood-forming cells of the bone marrow. Leukemia results from an abnormal development of leukocytes (white blood cells) and their precursors. Leukemia cells look different than normal cells and do not function properly.

Description

There are four main types of leukemia, which can be further divided into subtypes. When classifying the type of leukemia, the first steps are to determine whether the cancer is lymphocytic or myelogenous (cancer can occur in either the lymphoid or myeloid white blood cells) and whether it is acute or chronic (rapidly or slowly progressing).

In acute leukemia, the new or immature cells, called blasts, remain very immature and cannot perform their functions properly. The blasts rapidly increase in number and the disease progresses quickly. Major types of acute leukemia include **acute lymphocytic leukemia** (ALL)

and **acute myelocytic leukemia** (AML; also known as acute myelogenous leukemia).

Kate Kretschmann

Acute lymphocytic leukemia

Definition

Acute lymphocytic leukemia is a cancer of the white blood cells known as lymphocytes.

Description

Leukemia is a cancer of white blood cells. In acute leukemia, the cancerous cells are immature forms called blasts that cannot properly fight infection; patients become ill in rapid fashion.

The cells that make up blood are produced in the bone marrow and the lymph system. The bone marrow is the spongy tissue found in the large bones of the body. The lymph system includes the spleen (an organ in the upper abdomen), the thymus (a small organ beneath the breastbone), and the tonsils (an organ in the throat). In addition, the lymph vessels (tiny tubes that branch like blood vessels into all parts of the body) and lymph nodes (pea-shaped organs that are found along the network of lymph vessels) are also part of the lymph system. The lymph is a milky fluid that contains cells. Clusters of lymph nodes are found in the neck, underarm, pelvis, abdomen, and chest.

The main types of cells found in the blood are the red blood cells (RBCs), which carry oxygen and other materials to all tissues of the body; white blood cells (WBCs), which fight infection; and the platelets, which play a part in the clotting of the blood. The white blood cells can be further subdivided into three main types: granulocytes, monocytes, and lymphocytes.

The granulocytes, as their name suggests, have particles (granules) inside them. These granules contain special proteins (enzymes) and several other substances that can break down chemicals and destroy microorganisms such as bacteria. Monocytes are the second type of white blood cell. They are also important in defending the body against pathogens. The lymphocytes form the third type of white blood cell. The two types of lymphocytes are B cells, which make antibodies, and T cells, which make other infection-fighting substances. Lymphocytic leukemia can arise in either B or T cells.

B-cell leukemia occurs more frequently than T-cell leukemia. It is the most common form of leukemia in children, but also occurs in adults. At diagnosis, leukemic cells can be found throughout the body, in the bloodstream, the lymph nodes, spleen, liver, occasionally in the central nervous system, and in T-cell ALL, the thymus gland.

Cancerous lymphoblasts take over the bone marrow, reducing both the number and the effectiveness of all types of blood cells. The cancerous cells reduce the ability of healthy white cells to fight infection. Fewer red cells are produced, causing **anemia**, and fewer platelets increases the risk of bleeding and bruising. The presence of the cancerous white cells in the central nervous system can produce headaches, confusion and seizures.

The type of treatment a person receives for ALL depends on the presence of risk factors for relapse. Children are at standard risk if they are between ages 1 and 9, have a total white cell count of less than 50,000 per microliter of blood, and have B-precursor cell leukemia. Children are at high risk if they are younger than 1 or older than 9, if their white blood cell count exceeds 50,000 per microliter, or if they have T-cell leukemia. Compared to children, adults are all at higher risk of relapse at the time of diagnosis, but younger adults (less than 25 years old) have a better prognosis.

B-cell ALL constitutes about 80% of all cases. The cancerous cells are either early pre-B cells, the most immature, pre-B cells, also somewhat immature, or B cells. These B-lineage cells contain a variety of proteins called antigens. The presence of one of these antigens, called CALLA for common ALL antigen, carries a somewhat more favorable prognosis.

T-cell ALL has a less favorable prognosis than B-cell ALL. The presence of an antigen called CD2 indicates a more favorable prognosis.

ALL is also classified by karyotype, which is the number and composition of a cell's chromosomes. Normal human cells contain 46 chromosomes. One chromosomal abnormality often seen in ALL is a translocation, in which a piece of one chromosome becomes attached to a different chromosome. Different translocations carry different prognoses. One translocation, labeled t(9;22) is also called the Philadelphia chromosome and is found in 5% of childhood ALL and 20% of adult ALL cases. The Philadelphia chromosome carries a somewhat less favorable prognosis.

The number of chromosomes found in the leukemic cells, particularly in children, also impacts prognosis.

The occurrence of more than 50 chromosomes in leukemic cells has a very favorable prognosis. Even the presence of one extra chromosome can be favorable. Children whose leukemic cells have fewer than 45 chromosomes are at highest risk of treatment failure.

Demographics

ALL is less common than AML in adults; about 1500 adults are diagnosed with ALL each year, compared to 10,000 diagnosed with AML. About 1000 adults die of ALL each year and the overall five-year survival rate for adults with ALL is 58%.

About 1500 cases of ALL are diagnosed in children under 18 each year in the United States. ALL is by far the more common form of leukemia in children. The death rate for children with ALL has dropped nearly 60% in the last 30 years. The overall five-year survival rate for children with ALL is now 80%. Still, leukemia causes more deaths in children under 15, about 550 per year, than any other disease.

In the United States, ALL is highest among Caucasians and lowest among Asian-Americans. The incidence of ALL is about 50% higher for men than for women. Death rates in leukemia patients are highest in African-Americans and Caucasians and lowest in Asians.

In children, the highest leukemia rates in the US occur among those of Filipino descent; next highest are white Hispanics, then non-Hispanic whites, and the lowest incidence in children is in African-Americans. Survival is higher for Caucasians than African-Americans. The survival rate for girls is slightly higher, in part due to the risk of relapse occurring in the testicles and in part because boys appear to have a slightly higher risk of bone marrow relapse.

Causes and symptoms

Causes

While specific causes for ALL are not known, there are some known risk factors, including ionizing radiation. Exposure to certain chemicals, particularly benzene (used in the manufacture of plastics, rubber, and some medicines), has also been associated with an increased risk of developing ALL. ALL incidence in adults increases with age.

The causes of ALL in children are also unknown. Certain inherited genetic abnormalities, such as Down syndrome, increase the risk. Some studies have shown prenatal exposure to ionizing radiation increases a child's risk of ALL. Some contaminants of tap water, such as trihalomethanes, chloroform, zinc, cadmium, and arsenic are associated with an increased risk. A number of reports suggested an increased risk of ALL among children who lived in proximity to high voltage power lines, but several later analyses suggested that was not true. Studies continue in efforts to disprove or confirm this possible connection. ALL is more common in children who are not firstborn and among those whose mothers took **antibiotics** during their pregnancies. Breastfeeding has been found to be protective.

Symptoms

ADULTS ALL in adults can cause any or all of the following symptoms:

- fevers, chills, sweats
- weakness, **fatigue**, shortness of breath
- frequent infections
- depressed appetite, weight loss
- enlarged lymph nodes
- easy bleeding or bruising
- rash of small, flat red spots (petechiae)
- bone and joint pain

Symptoms of central nervous system involvement include:

- headache
- **nausea and vomiting**
- confusion
- seizures

CHILDREN Symptoms in children are similar, but young children may be unable to communicate them. They include:

- fevers
- frequent infections
- fatigue, irritability, decreased activity levels
- easy bruising or bleeding
- bone or joint pain
- a limp
- swollen belly
- enlarged lymph nodes

T-cell ALL can invade the thymus gland in the upper chest, which can cause compression of the windpipe, cough or shortness of breath, and **superior vena cava syndrome** (compression of a large vein that causes swelling of the head, neck, and arms).

Central nervous system involvement in children produces:

- headache
- nausea and vomiting
- blurred vision
- decline in school performance
- seizures

Spread to the testicles can cause painless swelling in them.

Diagnosis

There are no screening tests for leukemia. The patient's history and physical examination raise the physician's suspicions, triggering orders for appropriate tests. Pallor, swollen lymph nodes, bleeding, bruising, pinpoint red rashes, and in children, a swollen abdomen, will suggest the diagnosis. Testing is similar for adults and children.

The first test is a complete blood count (CBC), examining red cells, platelets and white cells. In early leukemia, the total white blood cell count might be normal, but there will usually be circulating lymphoblasts, which is always abnormal. The red cell and platelet counts may be low.

The abnormal CBC results trigger a referral to a hematologist/oncologist who will perform a **bone marrow aspiration and biopsy**, in which a small sample of marrow is removed with a hollow needle inserted in the hipbone. Although topical anesthetic will numb the skin and bone, most patients experience brief pain during this procedure. The sample will be examined microscopically for evidence of lymphoblasts. The marrow will be further studied to determine whether the lymphoblasts are of T-cell or B-cell origin and the cells tested for chromosomal abnormalities. A pathologist can examine the marrow and make the diagnosis immediately. The chromosome studies require several days to complete. The bone marrow aspirate will be repeated occasionally during treatment to confirm remission and to look for possible relapse.

A **lumbar puncture**, or spinal tap, will be performed to rule out spread of ALL to the central nervous system. A thin needle is inserted between two vertebrae in the lower back, and spinal fluid removed. This fluid is examined microscopically for the presence of lymphoblasts. Topical anesthetics eliminate most of the discomfort of a spinal tap, although many patients experience headaches afterwards. Remaining flat for 30 minutes after a spinal tap decreases the likelihood of headache.

A chest **x ray** will show enlargement of internal lymph nodes or the thymus gland.

No preparation is necessary for most of the testing done to diagnose ALL. Younger children will often receive mild sedatives before procedures like spinal taps and bone marrow studies. Topical anesthetic cream can be applied an hour in advance of either a bone marrow test or a spinal tap.

When treatment is complete, tests for minimal residual disease can be performed. These new tests detect the presence of lingering leukemic cells that would have been missed by standard testing. The presence of a certain amount of residual disease probably has an impact on prognosis and the likelihood of relapse.

Treatment team

The treatment team consists of a hematologist/oncologist who directs care, oncology nurses familiar with administering **chemotherapy**, and often social workers, who can address both insurance issues and psychological support. The patient's regular physician should be kept informed of all cancer-related care. Because treatment is so prolonged, most patients have long-term intravenous catheters placed by a surgeon.

In many hospitals, a Child Life specialist will participate in the care of children with ALL. They ensure that children with cancer are seen, first and foremost, as children, organizing play times, providing distraction during scary procedures and giving parents some much-needed respite.

Clinical staging, treatments, and prognosis

ALL does not have a formal staging system, but treatment is different in different phases of the disease. These phases are often divided into untreated ALL, ALL in remission, and recurrent ALL. Conventional treatment for ALL consists of chemotherapy for disease in the bone marrow and treatment aimed at preventing central nervous system disease.

ADULTS The first phase of treatment is remission induction. The chemotherapeutic drugs typically include prednisone, **vincristine**, **cytarabine**, **cyclophosphamide** and **asparaginase**. Most are given intravenously and a few are given orally. Depending on the disease, these drugs can achieve a complete remission in 60% to 90% of adults. The relapse rate is higher in adults than in children. A 50% 3-year survival has been noted in some research series, and very aggressive treatment with multiple drugs has produced up to a 70% survival rate.

Adverse effects of these drugs include:

- bone marrow suppression
- anemia, pallor, fatigue, shortness of breath, and angina in older patients
- bleeding, bruising
- increased risk of infection
- hair loss (**alopecia**)
- mouth sores
- nausea and vomiting
- menopausal symptoms
- lower sperm counts
- **tumor lysis syndrome**, in which the dead cancer cells can harm healthy organs

Treatment that is directed at preventing central nervous system spread is called prophylactic. Because of the blood brain barrier, a physical and chemical barrier that prevents toxins from reaching the brain and spinal cord, chemotherapeutic drugs do not easily reach the central nervous system. Thus, chemotherapeutic drugs are administered directly into spinal fluid, which circulates around the brain and spinal cord. This is called intrathecal chemotherapy. The drugs are given by spinal tap or through an **Ommaya reservoir**, which is surgically inserted under the scalp. This reservoir empties into the spinal fluid around the brain.

Some patients receive prophylactic **radiation therapy** to the brain, in addition to or instead of intrathecal chemotherapy.

CHILDREN The treatment of ALL in children represents one of the great success stories of modern oncology. In contrast to adults, most children with cancer enter into research protocols, strict treatment regimens with careful follow-up that are built on the most successful aspects of earlier treatments. Childhood ALL now has an 80% long-term survival rate, due in large part to the extensive and widely disseminated research on the disease. Within the United States, research on ALL was conducted for many years under the auspices of either the Children's Cancer Group or the Pediatric Oncology Group. In 1998, recognizing the benefits of cooperation and collaboration, these two groups joined forces with the National **Wilms' Tumor** Study Group and the Intergroup **Rhabdomyosarcoma** Study Group to form the Children's Oncology Group.

Remission induction chemotherapy for children includes vincristine, a steroid, and asparaginase. Children at higher risk of relapse are often given daunomycin as well. The adverse effects of these drugs include bone marrow suppression, risk of infection, nausea, vomiting, hair loss, and mouth sores. Although these drugs can reduce sperm counts, most survivors of childhood ALL grow up to have normal fertility. The drugs can be administered intravenously or as oral preparations. Oral prednisone has a particularly unpleasant taste that is hard to disguise and parents must be vigilant to ensure that their children are taking their proper doses.

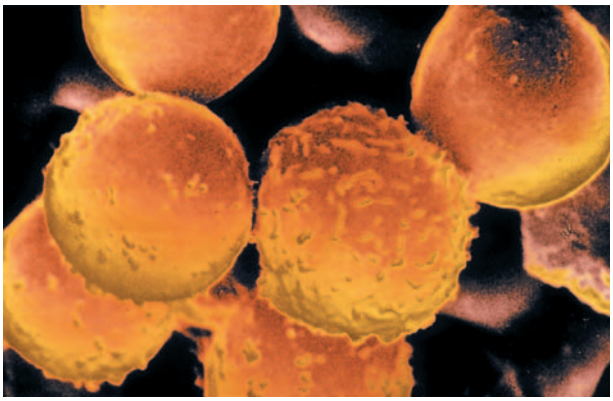
Like adults, children also receive prophylaxis against central nervous system spread. They receive multiple doses of intrathecal chemotherapy, with the drugs delivered directly to the spinal fluid through a lumbar puncture or spinal tap. Cranial radiation as central nervous system prophylaxis for children is infrequently used. Though once standard, brain radiation produced a high incidence of cognitive and learning disabilities, especially among those younger than five years old. Cranial radiation is reserved for those children felt to be at high risk of central nervous system disease, including those older than ten at the time of diagnosis, those with initial white blood cell counts of more than 50,000 per microliter, and those with T-cell leukemia. Some high-risk children who enter remission rapidly with induction chemotherapy receive intrathecal chemotherapy alone, without radiation therapy.

Alternative and complementary therapies

ADULTS Individuals with leukemia often employ alternative or complementary therapies. Some of these provide pain relief and improve psychological well being. No controlled studies have yet shown that alternative treatments offer cures for ALL, although some may hold promise of benefit.

Patients with ALL sometimes use acupuncture, which offers relief from generalized pain, nausea, and vomiting. Other methods that may help with the physical and often emotional side effects of treatment include hypnosis, guided imagery, and yoga.

Nutritional supplements and herbs are sometimes utilized by persons with leukemia. Coenzyme Q10 is an antioxidant, a substance that protects cells from toxic byproducts of metabolism. Early studies suggest, although it is not proven, that coenzyme Q10 can improve immune function and counteract some of the harmful effects of chemotherapy and radiation on healthy cells. Adverse effects of coenzyme Q10 include headache, rash, heartburn and **diarrhea**. Another supplement with potential benefit is polysaccharide K (PSK). A few studies have shown PSK to have some benefit in improving immunity.



False-color scanning electron micrograph (SEM) of white blood cells from a patient with acute lymphocytic leukemia. In this disease, certain types of white blood cells are overproduced, and these abnormal cells suppress the normal function of white and red cells, increasing the susceptibility to infections. *(Copyright Aaron Polliack, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Supplements that have not been proven to be of value or are potentially dangerous to those with leukemia include camphor, sometimes called 714-X. Green tea has received much press for its reported abilities to enhance the immune system and fight cancer, but studies have had conflicting results. Some show that green tea has preventive benefits and others show no effect. A few animal studies suggest that growth of tumors might be slowed by green tea, but this has not been shown in humans yet.

Hoxsey is another supplement touted as a cancer treatment, but no studies have confirmed any benefit. Some of its ingredients have serious adverse effects. Vitamin megadoses have long been advocated as beneficial in cancer, but no conclusive studies show benefit, and they have significant potential for adverse effects, such as diarrhea, kidney stones, iron overload, nerve damage and liver disease.

Laetrile, or amygdalin, was once touted as a cure for cancer and leukemia. No human or animal studies conducted in the decades since have shown any benefit other than relief of some pain. Laetrile can, however, cause cyanide poisoning.

CHILDREN Complementary and alternative treatments are recommended less frequently for children. Real caution must be used in administering herbal remedies to children, whose metabolisms are very different from those of adults. For example, jin bu hua, a traditional Chinese medicine, can cause heart or breathing problems. Life root and comfrey can both cause fatal liver damage in children.

While many children are too young for formal guided imagery, they can be distracted from the fears and pain associated with some treatments by toys and videotapes. Reading favorite books during scary procedures can relieve some of their fears.

ALL in remission

ADULTS Remission is achieved in many people within days of beginning treatment. Treatment does not end at that point, but rather enters into the next phases, called consolidation and maintenance. Several different approaches can be used in these. Some patients receive long term chemotherapy with drugs that might include Ara-C (cytarabine), cyclophosphamide, **methotrexate**, **mercaptopurine**, vincristine, prednisone, or **doxorubicin**. Other patients undergo high-dose chemotherapy or combination chemotherapy and radiation therapy to ablate or wipe out their own bone marrow, and then have bone marrow or stem cell transplants. Adverse effects of bone marrow transplant include significant risk of serious infection and **graft-vs.-host disease** (GVHD), in which the transplanted cells fail to "recognize" the host's cells as self and attack the host cells. Medications to decrease this risk include those that suppress the immune system and steroids.

Central nervous system prophylaxis, as either intrathecal chemotherapy or radiation therapy or both, typically continues through at least a portion of the post-remission therapy.

Adults who receive intensive chemotherapy have a 40% likelihood of long-term survival.

CHILDREN In children, remission induction therapy is followed by a phase termed consolidation or intensification, and then by a phase termed maintenance. During intensification, children receive intermediate or high-dose methotrexate, plus some of the same drugs that are used in induction, new drugs that do not cross-react with those used in induction, high-dose asparaginase, or some combination of these.

The maintenance phase of treatment for children with ALL continues for 18 to 30 months. Daily oral 6-mercaptopurine and weekly oral or injected methotrexate are given on an outpatient basis, with frequent blood tests and examinations. Some protocols add pulses of vincristine and prednisone during the maintenance phase.

Recurrent ALL

ADULTS Adults who relapse after initial remission and maintenance therapy often undergo reinduction chemotherapy and are then referred for bone marrow or stem cell transplant. Some receive transplants of umbilical cord blood. Such transplants carry the risk of graft

versus host disease, but also carry the possibility of graft versus leukemia, in which the transplanted cells attack the residual leukemic cells. Unlike graft versus host disease, graft versus leukemia is useful.

New treatments for relapsed ALL include immunotherapies or biological response modifiers. Some reduce adverse effects of treatment and others are used to fight the leukemia. Some of these include cytokines, substances that stimulate the production of blood cells after treatment has suppressed the bone marrow, and colony-stimulating factors, which have the same effect. Other immunotherapies, such as **monoclonal antibodies** and interferon, have not yet been shown effective against ALL, but are still under study.

CHILDREN The treatment and prognosis of children who relapse depends on the timing of that relapse. Relapse that occurs within six months is often treated with **bone marrow transplantation**. Early relapse carries the least favorable prognosis, with only 10% to 20% chance of long term survival. Relapse that occurs more than a year after initial treatment is finished can be treated with another full round of chemotherapy, and bone marrow transplant reserved for those children who relapse a second time. Those with such late relapses have a 30% to 40% chance of long term survival.

Recurrent disease may occur in a sanctuary site, or a part of the body difficult to penetrate with chemotherapeutic drugs. The central nervous system is the most common site of such recurrences. Children who have an isolated central nervous system relapse during the first 18 months of treatment have a 45% likelihood of long-term survival. Children with central nervous system relapse after the first 18 months of treatment have up to an 80% chance of long-term survival. Treatment for relapse in the central nervous system includes intrathecal chemotherapy, and for most children, the use of radiation therapy to the brain and spinal cord.

The testicles are the second most common site of relapse. Early testicular relapse (within the first 18 months of treatment) carries a 40% chance of long-term survival, and late testicular relapse carries an 85% chance of long-term survival. Another sanctuary site is the eye, but isolated relapse here is unusual.

Coping with cancer treatment

The treatment of ALL can be particularly draining, not only due to adverse effects but due to its prolonged time course. Although much of the treatment can be given on an outpatient basis, many protocols utilize lengthy intravenous infusions of chemotherapy and require hospitalization.

KEY TERMS

Antiangiogenic drugs—Drugs that block the formation of new blood vessels.

Blasts—Immature blood cells.

CBC—Complete blood count, a blood test that measures red cells, white cells and platelets.

Graft versus host disease—After bone marrow transplant, the newly transplanted white blood cells can attack the patient's own tissues.

Intrathecal chemotherapy—Chemotherapeutic drugs instilled directly into the spinal fluid, either by spinal tap or through a special reservoir.

Karyotype—The number and type of chromosomes found within cells.

Lymphoblasts—The cancerous cells of ALL, immature forms of lymphocytes, white blood cells that fight infection.

Ommaya reservoir—A special device surgically placed under the scalp with a direct connection to spinal fluid. Medications to treat central nervous system disease are injected into the reservoir.

Petechiae—Pinpoint red spots seen on the skin with low platelet counts.

Philadelphia chromosome—An abnormal chromosome found in 20% of adults and 5% of children with ALL, the presence of which indicates a somewhat worse prognosis.

Sanctuary sites—Areas within the body which are relatively impermeable to medications such as chemotherapy but which can harbor cancerous cells. Some of these sites are the central nervous system, the testicles, and the eyes.

Thymus—A gland within the chest involved in the maturation of immune cells that can be invaded by T lymphocytes in T-cell ALL.

ADULTS To prevent **nausea and vomiting**, adults can take oral anti-nausea medication an hour or so before scheduled treatments, including intrathecal treatments. To avoid headache, they should remain flat for at least 30 to 60 minutes after intrathecal chemotherapy. Nurses can give instructions in mouth care if mouth sores occur and skin care if rashes occur after radiation treatment. Books, music, and television can provide distraction and reduce anxiety during chemotherapy infusions.

Patients scheduled for inpatient stays can bring their own pillows, pajamas and even food, with their doctor's

approval. Temporary issuance of handicapped parking stickers are often helpful.

CHILDREN The presence of parents during treatment is critical. While some hospitals exclude parents during treatments, others invite them to be present. Blood can be drawn and intravenous catheters placed while children sit in their parents' laps. If at all possible, a parent should spend the night during any hospitalizations.

Like adults, children can take anti-nausea drugs an hour or so before scheduled treatments. Children, and some adults, can apply topical anesthetic creams to sites of bone marrow aspirates or spinal taps. Favorite stuffed animals or blankets can be present for most procedures.

Play and fun are as important to children with cancer as to healthy children. Items such as board games, modeling clay, video games, dolls, and toy cars can be enjoyed even with intravenous lines in place. Play dates with friends should be encouraged, with proper screening to limit exposure to contagious illnesses.

School districts are required to accommodate the special needs of children. Children with ALL might require shorter school days or the provision of a tutor at home. Children who develop learning disabilities due to treatment might require the intervention of a special education team.

Clinical trials

There are numerous **clinical trials** looking at novel strategies for the treatment of ALL in adults and children. Most oncologists consider bone marrow transplants to be state-of-the-art in specific circumstances, and some insurance companies agree. Many still require extensive reviews before approving coverage for transplant.

A variety of biological agents are currently under study. These include antibodies that react specifically against leukemic cells, causing their death, and chemicals that interfere with the leukemic cells' normal DNA function or their ability to make proteins.

Researchers are developing second and third generation versions of established chemotherapeutic drugs, isolating the molecular components of those drugs that seem to be most useful in ALL and amplifying them. Some of these drugs include 9-aminocamptothecin, aminopterin, annamycin, Ara-G, codrycepin, decitabine, and **trimetrexate**. Quinine shows promise in reducing the incidence of **drug resistance** that is sometimes seen in leukemic cells.

Locating and enrolling in clinical trials has been made easier by listings on the Internet. A general search under "clinical trials and leukemia" will yield several listings. University-affiliated hospitals and oncologists participate in many trials and can refer patients to other sites if necessary.

QUESTIONS TO ASK THE DOCTOR

- What type of leukemia do I or does my child have?
- What characteristics of my or my child's illness are favorable? Which are unfavorable?
- What course of therapy do you recommend?
- What medications will you use and what side effects are anticipated?
- Will I or my child need to be hospitalized for those treatments?
- Should I or my child be enrolled in a clinical trial?
- Can I continue to work or can my child go to school?
- Can I stay with my child for procedures? For hospitalizations?
- How and what should we tell our child about this illness?
- What should we tell our other children?

Prevention

There are few preventive measures to take against ALL. Those who work with chemicals should be cautious, particularly around benzene. Pregnant women should avoid exposure to ionizing radiation to reduce the risk to their unborn children.

Special concerns

Parents of children with ALL have specific concerns regarding the long-term consequences of treatment for ALL, such as learning disabilities. Organizations devoted to childhood cancer, hospital social workers, pediatric oncologists and other parents can be important resources when advocating for the educational needs of the child with ALL.

When cranial radiation must be used, children have a risk of developing secondary cancers in the central nervous system years later. Some children are left infertile by the treatment. Chicken pox can be lethal in children with ALL. The introduction of the chicken pox vaccine has reduced this risk, but parents must still be vigilant.

Resources

BOOKS

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Lackritz, Barb. *Adult Leukemia: A Comprehensive Guide for Patients and Families*. Sebastopol, CA: O'Reilly & Associates, 2001.

Patenande, Robert. *Surviving Leukemia: A Practical Guide*. Quebec: Firefly Books, Ltd., 1999.

PERIODICALS

Gaynon, P.S., et al. "Children's Cancer Group Trials in Childhood Acute Lymphoblastic Leukemia: 1983–1995." *Leukemia* 14, no. 5 (December 2000): 2223–33.

Hasle, H., et al. "Risks of Leukaemia and Solid Tumours in Individuals with Down Syndrome." *The Lancet* 355, no. 9199 (January 2000): 165–9.

Pui, C.H. "Acute Lymphoblastic Leukemia in Children." *Current Opinions in Oncology* 12, no. 1 (January 2000): 3–12.

ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd., Atlanta, GA, 30329. (800) ACS-2345. <http://www.cancer.org>.

Cancer Care, Inc. 1180 Avenue of the Americas, New York, NY 10036. (212) 302-2400 or (800) 813-4673. <http://www.cancercare.org>.

Candlelighters Childhood Cancer Foundation. 7910 Woodmont Ave., Suite 460, Bethesda, MD 20814. (800) 366-CCCF. <http://www.candlelighters.org>.

The Leukemia and Lymphoma Society of America (formerly The Leukemia Society of America). 1311 Mamaroneck Ave., White Plains, NY 10605. (914) 949-5213. <http://www.leukemia-lymphoma.org>.

The National Cancer Institute. Cancer Information Service. Building 31, Room 10A31, 31 Center Dr., MSC 2580, Bethesda, MD 20892-2580. (301) 435-3848. <http://www.nci.nih.gov/>.

National Childhood Cancer Foundation. 440 E. Huntington Dr., P.O. Box 60012, Arcadia, CA 91066-6012. (626) 447-1674. <http://www.nccf.org>.

National Marrow Donor Program. Suite 500, 3001 Broadway St. NE, Minneapolis, MN 55413-1753. (800) MARROW-2. <http://www.marrow.org/>.

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GrannyBarb and Art's Leukemia Links. [cited July 9, 2001]. <http://www.acor.org/diseases/hematology/Leukemia/leukmain.html>.

International clinical trials listings. [cited July 9, 2001]. <http://www.graylab.ac.uk/cancerweb/trials.html>.

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Patient-centered Guides. <http://www.patientcenters.com/leukemia>.

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Marianne Vahey, M.D.

Acute myelocytic leukemia

Definition

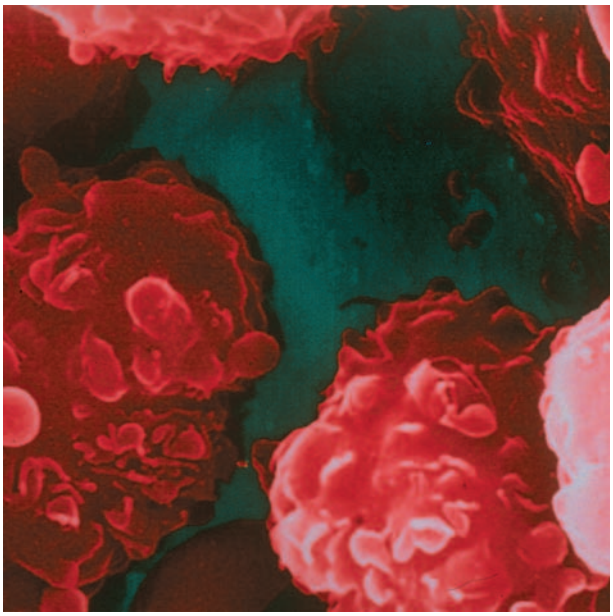
Acute myelocytic leukemia (AML) is an acute cancer that affects white blood cells, primarily those of the granulocyte or monocyte types.

Description

Acute myelogenous leukemia and acute nonlymphocytic leukemia (ANLL) are other names for AML and refer to the identical disease.

The cells that make up blood are produced in the bone marrow and the lymph system. The bone marrow is the spongy tissue found in the large bones of the body. The lymph system includes the spleen (an organ in the upper abdomen), the thymus (a small organ beneath the breastbone), and the tonsils (an organ in the throat). In addition, the lymph vessels (tiny tubes that branch like blood vessels into all parts of the body) and lymph nodes (pea-shaped organs that are found along the network of lymph vessels) are also part of the lymph system. The lymph is a milky fluid that contains cells. Clusters of lymph nodes are found in the neck, underarm, pelvis, abdomen, and chest.

The main types of cells found in the blood are the red blood cells (RBCs), which carry oxygen and other materials to all tissues of the body; white blood cells



An enhanced scanning electron microscopy (SEM) image of acute myelocytic leukemia cells. *(Photograph by Robert Becker, Ph.D., Custom Medical Stock Photo. Reproduced by permission.)*

(WBCs), which fight infection; and the platelets, which play a part in the clotting of the blood. The white blood cells can be further subdivided into three main types: granulocytes, monocytes, and lymphocytes.

The granulocytes, as their name suggests, have particles (granules) inside them. These granules contain special proteins (enzymes) and several other substances that can break down chemicals and destroy microorganisms such as bacteria. Monocytes are the second type of white blood cell. They are also important in defending the body against pathogens. The lymphocytes form the third type of white blood cell.

The bone marrow makes stem cells, which are the precursors of the different blood cells. These stem cells mature through stages into either RBCs, WBCs, or platelets. In acute leukemias, the maturation process of the white blood cells is interrupted. The immature cells (or "blasts") proliferate rapidly and begin to accumulate in various organs and tissues, thereby affecting their normal function. This uncontrolled proliferation of the immature cells in the bone marrow affects the production of the normal red blood cells and platelets as well.

Acute leukemias are of two types: **acute lymphocytic leukemia** and acute myelogenous leukemia. Different types of white blood cells are involved in the two leukemias. In acute lymphocytic leukemia (ALL), it is the lymphocytes that become cancerous. AML is a cancer of the monocytes and/or granulocytes.

The reason certain leukemias are now called acute is because of names received decades ago. Before the discovery of modern methods of cancer treatment, these were illnesses that progressed rapidly. In contrast, chronic leukemias were, in this period before newer methods had been invented, illnesses that progressed more slowly.

Demographics

Approximately 23 new cases of AML appear per each million Americans each year. Men are somewhat more likely to develop AML than are women. Approximately 29 new cases appear per every million males while approximately 19 new cases appear per every million females per year.

Older persons are considerably more likely to develop AML. Approximately 13 people per million younger than 65 years of age will develop AML. In contrast, 122 people per million older than 65 years of age will develop the disease.

AML sometimes affects children. About 500 children develop AML in the United States every year. Approximately one in five of all children who develop leukemia develop AML. The disease affects boys and girls in roughly equal numbers. Children of all ethnic groups may develop the disease. If one of two identical twins develops AML, the chances are considerable that the other twin will develop it as well.

Causes and symptoms

AML is neither contagious nor inherited. However, people who suffer from certain genetic disorders, such as **Fanconi anemia**, Klinefelter syndrome, Patau syndrome, Bloom syndrome, and Down syndrome, are at greater risk of developing AML than the general population. A child with Down syndrome is roughly 14 times as likely as the average child to develop leukemia.

Any person who has been exposed to radiation at high doses is at heightened risk of developing AML, as are people exposed to benzene, a chemical used in the manufacture of plastics, rubber, medicines, and certain other chemicals. Another group of people at increased risk for developing AML are those who have been treated for cancer with certain medicines, for example, chloramphenicol, phenylbutazone, chloroquine, and methoxypsoralen.

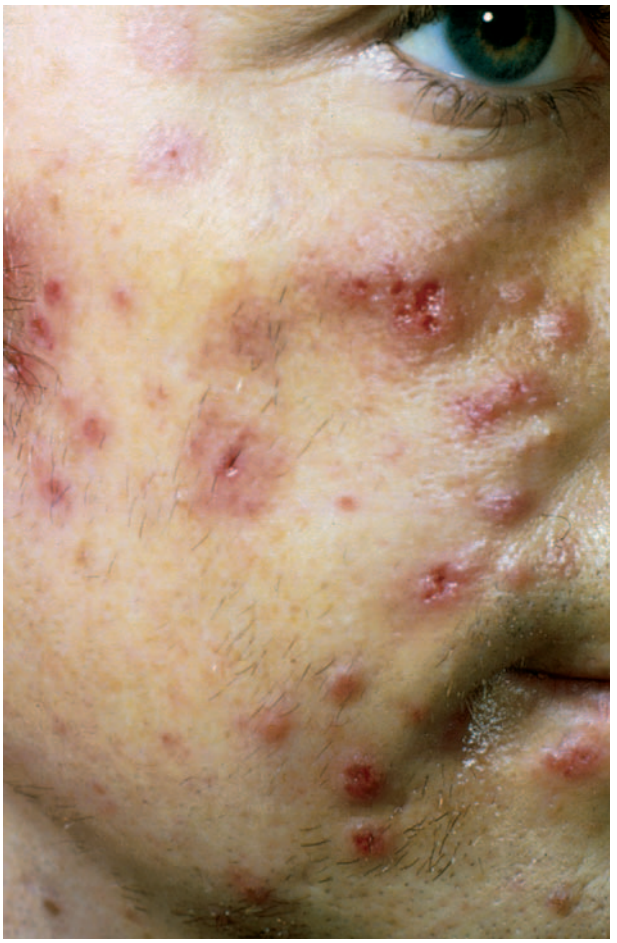
The symptoms of AML are generally vague and non-specific. A patient may experience all or some of the following symptoms:

- weakness or chronic **fatigue**

- **fever** of unknown origin
- shortness of breath
- weight loss that is not due to dieting or exercise
- frequent bacterial or viral infections
- headaches
- skin rash
- non-specific **bone pain**
- easy bruising
- bleeding from gums or nose
- blood in urine or stools
- enlarged lymph nodes and/or spleen
- abdominal fullness

A small minority of patients with AML have a tumor of leukemic cells at diagnosis. Such a tumor may appear in the lung, breast, brain, uterus, ovary, stomach, prostate, or certain other places in the body.

Some children with AML present to their doctor with very few symptoms, while other children present with severe symptoms. **Anemia** is usually present. The symptoms of the anemia may include fatigue, dizziness, headache, paleness of the skin, or, infrequently, congestive heart failure. Easy bruising, bleeding gums, and nosebleeds may be present, as may fever. There may be swollen gums, bone pain or joint pain, or, rarely, an actual tumor. Some infants with AML have skin disorders.



An acute myelocytic leukemia patient with a rash, one of the symptoms of the disease. *(Custom Medical Stock Photo. Reproduced by permission.)*

Diagnosis

Like all cancers, acute leukemias are best treated when found early. There are no screening tests available.

A thorough diagnostic evaluation should be conducted. This is important because the doctor must determine more than whether or not AML is present. If it is suspected, has it affected the general health of the patient? Is the patient capable of undergoing rigorous treatment?

A doctor who suspects leukemia may start by obtaining a thorough medical history. The doctor may then conduct a very thorough physical examination to look for enlarged lymph nodes in the neck, underarm, and pelvic region. Swollen gums, enlarged liver or spleen, bruises, or pinpoint red rashes all over the body are among the signs of the disease. In addition, the physician may examine the teeth and look for dental abscesses, and may explore whether back pain is present.

Urine and blood tests may be ordered to check for microscopic amounts of blood in the urine and to obtain a complete differential blood count. This count will give the numbers and percentages of the different cells found in the blood. An abnormal blood test might suggest leukemia. Patients suffering from AML may have high leukocyte counts and typically have low counts of both red blood cells and platelets. Many patients with AML have low counts of all of the major components of the blood. A microscopic exploration of the blood will usually show that leukemic blast cells are present. However, the diagnosis has to be confirmed by more specific tests.

The doctor may perform a **bone marrow aspiration and biopsy** to confirm the diagnosis of leukemia. Aspiration involves the withdrawal of a liquid sample of marrow. During the **biopsy**, a cylindrical piece of bone and marrow is removed. The tissue is generally taken out of the hipbone. These samples are sent to the laboratory for examination. In addition to diagnosis, the aspiration and biopsy may be repeated during the treatment phase of the disease to see if the leukemia is responding to therapy.

A chest **x ray** is taken. Cardiac tests, including an electrocardiogram, are conducted. The patient is examined for possible infection. These diagnostic procedures often disclose bleeding in the stomach or intestines, and there may be bleeding in the lungs, brain, or eyes. Anemia is often present and may be severe.

Cytogenetic studies, which examine the number and shape of the chromosomes in the DNA of individual blast cells, should be conducted in addition to the immunophenotyping of cells of the bone marrow. This procedure involves applying various stains to the marrow cells. These stains help doctors identify some of the proteins lying on the surface of the cells.

A spinal tap (**lumbar puncture**) is another procedure the doctor may order to diagnose leukemia. In this procedure, a small needle is inserted into the spinal cavity in the lower back to withdraw some cerebrospinal fluid and to look for leukemic cells.

Standard imaging tests such as x rays may be used to check whether the leukemic cells have invaded other areas of the body, such as the bones, chest, kidneys, abdomen, or brain. Other tests, such as **computed tomography** scans (CT scans), **magnetic resonance imaging** (MRI), or gallium scans, are not typical for AML but may also be performed.

Children with AML are given most of the same studies used for adults.

Clinical staging, treatments, and prognosis

Unlike several other cancers, AML is not staged. However, a classification system is used to separate different forms of AML. One of the most important classification systems, devised by a team of physicians, is known as the French-American-British (FAB) Classification System.

The goal of AML treatment is to achieve a complete remission (CR). What is a complete remission? It is a measure that indicates that the patient's disease has gotten markedly better in several ways. In general, it might be said that CR is achieved once the body has regained its ability to produce blood cells normally. At this point, the number of blood cells of various types should return to normal ranges, while none of the immature cells called leukemic blast cells should be present in the blood or the marrow.

Chemotherapy is the use of drugs to kill cancer cells. It is usually the treatment of choice and is used to relieve symptoms and achieve long-term remission of the disease. Generally, combination chemotherapy, in which multiple drugs are used, is more efficient than using a single drug for the treatment. Some drugs may be administered intravenously through a vein in the arm; others may be given by mouth in the form of pills. If the cancer cells have invaded the brain, then chemotherapeutic drugs may be put into the fluid that surrounds the brain and spinal cord. This is known as intrathecal chemotherapy. Chemotherapy should start soon after diagnosis.

KEY TERMS

Blasts—An immature cell.

Bone marrow—Spongy tissue found in the large bones of the body.

Cytogenetic testing—Analysis of parts of the nucleus of blast cells.

Granulocytes—White blood cells containing particles or granules.

Immunophenotype—A test that involves placing various sorts of stains on bone marrow cells to help identify the chemicals located on the cell surfaces.

Monocytes—Another type of white blood cell, important in the defense against pathogens.

Patients who are anemic or who have low platelet counts should receive transfusions. These transfusions should be sufficient to restore counts of various components of the blood to adequate levels.

There are two phases of treatment for leukemia. The first phase is called induction therapy. During this phase, the main aim of treatment is to reduce the number of leukemic cells as much as possible and induce a remission in the patient. A variety of chemotherapy agents may be used during the induction therapy portion of AML treatment. In 2001, the chemotherapy agent Ara-C (**cytarabine**) is often used in combination with either **daunorubicin** or **idarubicin** (Idamycin). Other doctors add **etoposide** to this combination of chemotherapy agents. For older patients, Ara-C and **mitoxantrone** may be used. Some patients benefit from receiving high doses of chemotherapy drugs. As of 2001,patients who do not achieve CR, as well as those who achieve CR but then relapse, may be given mitoxantrone plus etoposide.

The second phase of treatment is initiated once CR is achieved. This is called post-remission or consolidation therapy. The goal of therapy now becomes killing any remaining cells and maintaining the remission for as long as possible. There are various ways of attempting to reach this goal. One involves additional chemotherapy. Another involves **bone marrow transplantation** (BMT), also called stem cell transplant (SCT). Trans-

plantation therapy has been studied very thoroughly. It involves taking blood-making cells, whether from the patient or from another person, and infusing them into the patient following removal of the diseased marrow, with either high doses of chemotherapy or total body irradiation. These procedures are potentially very effective because of the remarkable ability of these cells to create a sustained replacement of the patient's blood cells. Other strategies may also be applied. Approaches used for patients younger than 60 years of age may differ from those used for patients of older ages.

Because leukemia cells can spread to all the organs via the blood stream and the lymph vessels, surgery is not considered an option for treating leukemias.

Children with AML also receive induction therapy. Often two or three medicines are used in conjunction with one another. After remission is achieved in a young patient, postremission therapy is started. The type of postremission therapy depends largely on the type of AML the patient has. It may involve additional chemotherapy or, alternatively, bone marrow transplantation. Chemotherapy to the central nervous system (CNS) is given to most children, since without it, roughly one in five will develop CNS relapse. The CNS includes the brain and spinal cord.

The prognosis of patients with AML varies. A number of different matters should be examined before the prognosis of any individual patient is assessed. The most important of these is whether or not the patient attains a complete remission (CR). The most important consideration in terms of whether a patient is likely to achieve CR is the patient's age. However, it may be that chronological age is not what really matters. Rather, to a large extent, what is truly significant is the patient's ability to survive the difficulties associated with induction therapy. For example, the patient who has some other disease in addition to AML may have a more difficult time with the rigors of the therapy. Yet, it is also true that older patients are more likely to have AML that expresses certain characteristics associated with poorer outcomes.

Other factors also affect the patient's prognosis. For example, in the tests performed during diagnosis, the chromosomes of cells are examined. Some chromosomal findings are associated with a good prognosis. Others are only mildly good, while still others indicate the patient is less likely to achieve CR.

Other factors that may provide physicians with hints as to the patient's prognosis include: how long symptoms were present before the illness was diagnosed, and how quickly immature blast cells disappear after treatment is started.

QUESTIONS TO ASK THE DOCTOR

- What type of AML do I have? What does it mean to have this variant of the disease?
- How can I obtain supportive care so I come through this not only alive but with my family and emotional life intact?
- Do I have any infections?
- What are the results of the cytogenetic testing?
- What are the results of the immunophenotyping?
- What is my prognosis?
- Are blasts present?
- Are blood counts returning to normal levels?
- Has complete remission been achieved?
- What can I do to lower my risk of infection during chemotherapy?

Coping with cancer treatment

One of the most important aspects of treatment is guaranteeing that the patient will have the supportive care needed to come through the treatment period with physical and emotional strength intact. Part of what this means is that AML should be treated in major cancer centers, because only these centers have the expertise necessary to provide not only the right medicine but also the accompaniments of good treatment.

One way physicians help AML patients cope with treatment is to guarantee that adequate blood bank support is available. Many patients require platelet transfusions.

One of the great dangers to patients during induction treatment and other steps of treatment is the threat of serious infectious disease. These patients have weakened blood components and are therefore more susceptible to infectious illness than the average person is. The leading cause of death for patients receiving induction treatment and chemotherapy following remission is infectious illness.

To help build the patient's white cell count, doctors may prescribe growth factors. These encourage the body to produce certain types of blood cells. The types of growth factors prescribed most frequently are granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF).

The psychological aspects of cancer treatment are a major concern. Patients should ask their physician about

local support groups and survivor networks that can help with the stresses associated with this disease.

Prevention

High doses of radiation and exposure to the chemical benzene (used in the manufacture of plastics, rubber, and medicines) are strong risk factors. With the exception of people with such rare genetic conditions as Fanconi anemia, Klinefelter syndrome, Patau syndrome, Bloom syndrome, and Down syndrome, there is no known genetic predisposition to AML.

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Lata Cherath, Ph.D.
Bob Kirsch

Acute myelogenous leukemia *see* **Acute myelocytic leukemia**

Acute promyelocytic leukemia *see* **Acute myelocytic leukemia**

Acyclovir *see* **Antiviral therapy**

Adenocarcinoma

Definition

Cancer that begins in the epithelial cells, which line certain internal organs and have glandular (secretory) properties. Some types of adenocarcinomas include cancers of the breast, thyroid, colon, stomach, pancreas, and prostate, as well as certain types of lung cancer.

Kate Kretschmann

Adenoma

Definition

A benign (noncancerous) tumor that forms from the cells lining the inside or the surface of an organ.

Description

Adenomas arise from cells that are specialized for secretion. These cells, called epithelial cells, are found throughout the body, but only a fraction is designed for secretion. This type of epithelial cell makes up specific organs and structures in the body known as glands. Glands produce sweat, saliva, mucus, milk, digestive juices, hormones, and an array of other substances. Hormone-secreting (endocrine) glands include the thyroid, pituitary, parathyroids, adrenals, and the ovaries and testes. Gland cells that secrete material outward through a duct, such as sweat glands and glands secreting digestive juices into the stomach and intestines, are called exocrine glands. Adenomas can arise from most of the gland cells in the body.

Adenomas result from excessive growth of normal epithelial cells. They arise in much the same way as malignant (cancerous) tumors but do not spread (metastasize) to nearby tissue or other parts of the body. New cells are normally created only when they are needed by

the body. When the body does not need new cells and cell division continues, a mass or tumor is formed.

Tumors found on some glands are more likely to be adenomas than malignant tumors (carcinomas), including **adrenal tumors**, **pituitary tumors**, and **salivary gland tumors**. The adrenal tumor known as **pheochromocytoma** is benign in 90% of reported cases. The gastrinomas associated with **Zollinger-Ellison syndrome** are benign in 50% of patients with this condition. Adenomas are also associated with **Cushing's syndrome**, a disorder caused by excess levels of a hormone secreted by the adrenal glands. Although most cases are caused by a dysfunctional pituitary gland, 20–25% are due to adrenal adenomas.

The occurrence of an adenoma rarely indicates an increased chance for the later development of a **carcinoma**. However, **colon cancer** and **rectal cancer** are thought to arise from adenomas, and one type of lung adenoma—called a bronchial adenoma—can potentially develop into lung cancer.

Most adenomas affect the normal functioning of the organ or gland in which it arises, although some have no effect. Many secrete hormones, leading to elevated hormone levels in the blood and causing uncomfortable and sometimes life-threatening conditions.

Demographics

Certain types of adenomas are more common in women than in men (e.g., pituitary tumors and liver adenoma), and some are more common in older adults (e.g., adenomas of the colon). But specific demographics depend on the specific type of adenoma.

Causes and symptoms

The cause of adenomas is often unknown. Liver adenomas in women are linked to the use of oral contraceptives, and some conditions, such as pheochromocytomas and colon adenomas, can be inherited.

No single set of symptoms can be applied to all adenomas. Some disorders have similar or identical symptoms whether due to an adenoma or carcinoma. Ultimately, the signs and symptoms depend on the location of the adenoma:

- Adrenal glands: an adrenocortical adenoma often shows the same symptoms of an **adrenocortical carcinoma**, including abdominal pain and loss of weight. A benign and malignant pheochromocytoma also has the same symptoms, including headaches, sweating, and chest pains.
- Breast: a marble-like benign fibroadenoma causes no symptoms and is either too small to detect by touch or is several inches across and easily detected.
- Colon or rectum: persistent **diarrhea** can indicate villous adenomas of the rectum. Blood in stool samples can indicate adenomas in the colon or rectum.
- Liver: a hepatic adenoma causes pain and a mass that is detectable by touch.
- Lung: a chronic or bloody cough, **fever**, chills, and shortness of breath can indicate a bronchial adenoma.
- Pancreas: pain in the abdomen, diarrhea, stomach pain, persistent fatigue, fainting, and weight gain can indicate one of the various types of pancreatic adenomas or pancreatic cancer.
- Parathyroid: weakness, **fatigue**, constipation, kidney stones, loss of appetite, and **bone pain** are signs of a condition known as hyperparathyroidism, which occurs in patients with parathyroid adenomas or parathyroid cancer.

KEY TERMS

Adrenal glands—Two glands, one located above each kidney, that secrete hormones to prevent inflammation and to help regulate blood pressure, blood sugar levels, and metabolism.

Carcinoma—A malignant (cancerous) tumor that forms from the cells lining the inside or the surface of an organ. They tend to spread to other tissues and organs.

Colon—A section of the large intestine, occurring before the rectum, that functions to absorb water and minerals from material that passed undigested from the small intestines.

Epithelium—A type of tissue that is composed of epithelial cells. It covers the outer and internal surfaces of the body and forms glands and parts of the sense organs.

Parathyroid glands—Four glands found in the neck area, with a pair on either side of the thyroid. They produce parathyroid hormone, which controls the level of calcium in the blood.

Pituitary gland—A small gland found at the base of the brain. It is an important endocrine gland because it secretes many different hormones that control the activity of other endocrine glands.

Thyroid gland—A gland located at the base of the neck. It secretes hormones that are essential for the regulation of body temperature, heart rate, metabolism, the level of calcium in the blood, and the level of calcium absorption by the bones.

- Salivary gland: adenomas are small and usually painless but can cause swelling around the chin or jawbone, numbness of the face, and pain in the face, chin, or neck.
- Stomach and intestine: a gastrinoma causes a peptic ulcer in the intestines or stomach. The occurrence of many ulcers in the stomach, intestine, and pancreas that do not respond well to treatment can indicate Zollinger-Ellison syndrome.
- Sweat gland: adenomas may appear as many small, smooth, and firm bumps on the lower eyelids and upper parts of the cheek (syringomas), or as small bumps with bluish or dark-brown coloration on the head and neck area (hidrocystoma). Solitary adenomas (poromas) occur on the sole of the foot or palm of the hand.
- Thyroid: a lump in the neck region accompanied by a cough and difficulty swallowing or breathing often indicates a benign thyroid nodule; however, these are the same symptoms for thyroid cancer.

Diagnosis

A variety of techniques is used to diagnose adenomas. Blood and urine samples are taken to detect elevated levels of hormones or other substances associated with a specific adenoma. Tumors are located using a combination of **ultrasonography**, **computed tomography** scan (CT scan), **magnetic resonance imaging** (MRI), and possibly radionuclide imaging. A **biopsy** is performed to determine whether a tumor is benign or malignant.

Treatment team

A doctor who interprets tissue samples (a pathologist) and a doctor trained in examining x rays and computer images (a radiologist) will make an initial diagnosis. Adenomas are often surgically removed, so a surgical team consisting of an anesthesiologist, surgeon, and nurses is often associated with treatment.

Clinical staging, treatments, and prognosis

Surgical removal is the recommended treatment for most adenomas, although the symptoms of some adenomas, such as pituitary tumors, can be treated with medication. In most cases, treatment cures the condition.

Clinical trials

Two **clinical trials** completed in mid-2001 investigated treatments to prevent colon cancer in patients who have had surgery to remove adenomas of the rectum or colon. An 800 mg daily dose of **folic acid** may decrease the occurrence of colon cancer in patients who have had adenomas removed. The combined use of two drugs that are prescribed for other conditions, eflonithine and sulindac, may prevent the development of adenomas or the recurrence of colon cancer.

QUESTIONS TO ASK THE DOCTOR

- Does the occurrence of this adenoma increase my chances of developing cancer?
- If I choose to have the adenoma surgically removed, what are the chances that I will develop another adenoma?
- Will all my symptoms disappear once the adenoma is removed?

See also Fibrocystic condition of the breast; Pancreatic cancer, endocrine; Pancreatic cancer, exocrine.

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Monica McGee, M.S.

Adjuvant chemotherapy

Definition

Adjuvant **chemotherapy** is cancer treatment that is administered after the primary therapy. For example, when the primary therapy to treat a cancerous tumor is surgery, chemotherapy would be an adjuvant therapy.

Purpose

Even if there is no clear sign that the cancer has spread, adjuvant chemotherapy is administered to pre-

vent the chance of a recurrence by killing any cancer cells that *may have*spread. The rationale behind adjuvant chemotherapy is that the chemotherapy drugs are more effective when they are given immediately after the tumor has been removed and any remaining cancer is in small amounts.

For some cancers, especially breast and colorectal cancers, adjuvant chemotherapy has been shown to decrease the chance the cancer will return. In addition, cancer patients who received adjuvant chemotherapy tend to live longer than those who do not receive the treatment.

Description

Patient selection

Patients selected for adjuvant chemotherapy are usually considered to have a high risk of recurrence. In order to determine the chance of recurrence, physicians look at the prognostic factors, which means they study the characteristics of the tumor. Tumor size, histology, and the proliferation rates are three prognostic factors that help determine the necessity for adjuvant chemotherapy. For example, patients with small tumors (2 centimeters or less) have a better prognosis, in general, than patients with large tumors (5 centimeters or more). Histology (or histologic grade) refers tow hat the tumor cells look like under a microscope. In other words, are the cells close to normal or are they far from normal. The term used to describe them is *differentiated*. When a tumor is well differentiated, the prognosis is better, because the cells closely resemble normal cells. When a tumor is poorly differentiated, the prognosis is considered to be not as good because the cells look very little like normal cells. A high proliferation rate refers to the rate in which cancer cells divide to make more cells. When the cancer cells are multiplying quickly, the cancer is described as aggressive, which often means adjuvant chemotherapy is needed.

Other prognostic factors may need to be considered, depending on the cancer type. For example, the degree of lymph node involvement is an important consideration when the patient has **breast cancer**. During the tumor surgery, physicians often remove some of the underarm lymph nodes to see if they contain any cancerous cells. Positive lymph nodes indicate a higher risk of recurrence, because research shows if the cancer has spread to the lymph nodes, it may have spread to other parts of the body. Hormone receptor status (high levels of estrogen or progesterone that affect cell growth) may also impact the decision whether or not to treat a patient with adjuvant chemotherapy. It should be noted, however, that a panel of experts at a conference sponsored by the National Institutes of Science concluded that "adjuvant chemotherapy improves survival [of breast cancer patients] and should be offered to most women with primary breast cancers (larger than 1 centimeter in diameter) regardless of tumor involvement in the lymph nodes under the arm, menopausal status, or hormone receptor status." Despite the value of analyzing prognostic factors, physicians cannot predict with 100% certainty what the outcome of adjuvant chemotherapy will be. Treatment decisions must be made on an individual basis, taking into account the patient's general health, as well as his or her preferences.

Treatment specifics

In general, adjuvant chemotherapy is started as soon as possible after surgery. In the case of colorectal cancer patients, for example, physicians don't like to wait more than six weeks after surgery to begin adjuvant chemotherapy. Chemotherapy regimes generally include more than one drug, but not always. The drug combinations are selected based on the kind of cancer being treated and individual patient considerations.

Adjuvant chemotherapy treatments are usually given over a period of months in cycles, meaning a treatment is followed by a recovery period. The treatments can be administered orally, intravenously (through a vein), by injection, or by a patch on the skin. Most patients receive adjuvant chemotherapy as an outpatient in a hospital or clinic, but, in some cases, the treatments can be given at home.

Preparation

Each patient should talk with his or her doctor regarding any preparations that need to be made prior to treatment. Patients who work outside the home might want to plan, if possible, to take the entire day off from work on the day the chemotherapy is given. Depending on how a patient responds to treatment, the patient may need the next day off as well. The laws vary from state to state regarding employee rights, but many states have specific laws that address what the obligations of an employer are to an employee who is seriously ill. Patients concerned that they might be treated unfairly should consult an attorney.

Many patients prefer to have someone with them when they receive chemotherapy treatments, especially with regard to driving them home. Some cancer treatment centers insist that a patient have someone provide transportation. Patients who do not have friends or family available to help them can call the American Cancer Society. They manage a volunteer program that provides cancer patients with rides to and from the hospital or clinical where they will receive their treatments. For patients that live over 30 miles away from the nearest treatment

center or hospital, the American Cancer Society also tries to arrange free-of-charge hotel rooms for cancer patients.

Patients with children may want to arrange to have someone stay with them while they are having chemotherapy, especially the day of or the day after the treatments. Patients should ask their physicians what local support groups exist in their area that specialize in this type of assistance. Church groups often have volunteers who will be willing to lend a hand as well. In addition, the hospital or cancer treatment center is likely to have a list of available services from a variety of sources.

Aftercare

Patients can expect to have some side effects associated with chemotherapy, although the particular side effects will vary depending on the patient and the drug combinations. Most patients lose their hair during chemotherapy treatment. Patients can also expect to be more prone to infection and feel fatigued, even for a period of time after the therapy is all done. For example, patients whose gums tend to bleed when they brush their teeth may be advised to brush their teeth gently and use a soft brush. Other cautions may be to avoid crowds and people who patients know are sick. Other common side effects are nausea, vomiting, **diarrhea**, and mouth sores.

Chemotherapy doses can be adjusted and medication can be prescribed to help the patient overcome nausea. Patients should refrain from taking any medications (over-the-counter or prescription) without first talking to their oncologist (a physician who specializes in cancer treatment). In general, it is a good idea for patients to talk with all their treatment team regarding the toxic effects associated with adjuvant chemotherapy.

Risks

There is some concern that woman over 70 years of age, for example, are more likely to develop severe side effects than younger women. However, in a large randomized clinical trial conducted by Muss and colleagues, which was published in the *Journal of the American Medical Association*, it was concluded that age alone was not a significant enough reason to avoid treating elderly women with adjuvant chemotherapy. In the study, the researchers tracked 6,487 breast cancer patients, all of whom had a high risk of recurrence, to see how they responded to high doses of chemotherapy. The study included 542 patients who were 65 years of age or older and 159 of them were 70 years of age and older. Although the researchers found that older patients did have a slightly higher risk of bad reactions to the chemotherapy, the researchers concluded that the risks did not outweigh the benefits of treatment.

QUESTIONS TO ASK YOUR DOCTOR

- Will I need assistance performing my daily tasks?
- Are there certain food limitations associated with chemotherapy treatment?
- What other options do I have if this treatment doesn't work?
- How soon will I be able to return to work?
- Are there any clinical trials I should join?

Results

Treatment results vary from patient to patient, depending on a variety of factors. However, research shows that the benefits of adjuvant chemotherapy often outweigh the risks, especially for patients with breast or colorectal cancers. A patient's physician will perform various tests to determine if the treatment is working, such as blood tests and physical examinations. Some patients think that the side effects provide some indication as to how the treatment is working. The truth is, however, that the severity or lack of severity of the side effects has nothing to do with the effectiveness of the treatment.

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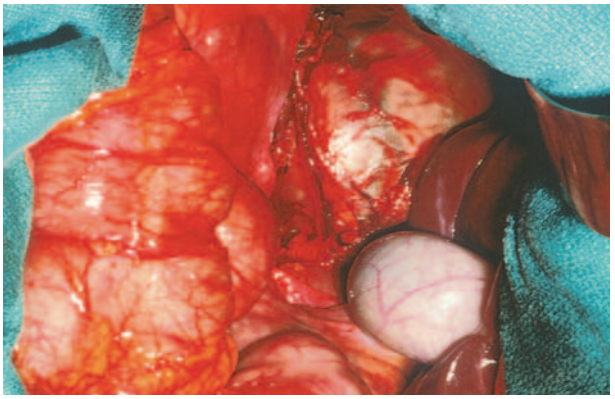
Lee Ann Paradise



An adrenal tumor is shown at lower left. The gallbladder is white, and the nearby liver is deep red. *(Custom Medical Stock Photo. Reproduced by permission.)*

Adrenal tumors

Definition

Tumors that occur on one or both of the adrenal glands.

Description

The two small adrenal glands, one located just above each kidney, are among the many endocrine (hormone-secreting) glands in the body. All endocrine glands make and store hormones. Hormones are chemical messages that are sent from an endocrine gland and are received by an organ or a cell to trigger a specific reaction. When the body requires hormone levels to rise, endocrine glands secrete them into the bloodstream. Adrenal gland tumors often cause overproduction of one or a combination of the adrenal hormones.

An adrenal gland has two parts, each of which secretes different hormones. The inner part is called the adrenal medulla, and the outer part is the adrenal cortex.

The adrenal medulla secretes the hormones epinephrine and norepinephrine. These hormones help maintain normal blood pressure. In high-stress situations, they help prepare the body for quick action by increasing heartbeat and breathing rate, increasing the flow of blood to the heart and lungs, and increasing blood pressure.

The adrenal cortex secretes aldosterone and cortisol. They also make small amounts of androgens, which affect the expression of female and male sex characteristics. Aldosterone helps maintain normal salt levels in the blood and the normal functioning of the kidneys. Cortisol (also called hydrocortisone) is the major adrenal hormone.

Cortisol is a steroid, an organic compound that affects metabolism. Many hormones and drugs used to relieve swelling and inflammation are steroids. Cortisol helps maintain blood pressure and is crucial in the breakdown of proteins, carbohydrates, and fats. It also raises blood sugar (glucose) when levels are too low, thus providing needed energy for the body's activities. Cortisol also prevents inflammation and is important for the normal response to stress.

The level of cortisol in the blood is carefully controlled. When the body needs cortisol, a small area of the brain called the hypothalamus releases coricotripoin-releasing hormone (CRH). The pituitary gland, located at the base of the brain, receives the message from the hypothalamus and begins secreting adrenocorticotropic hormone (ACTH). ACTH is received by the cortex of the adrenal glands, which responds by producing cortisol. When the level of cortisol meets the body's need, the pituitary stops producing ACTH, which then stops the adrenal cortex from secreting cortisol.

About 8% of people worldwide develop benign (noncancerous) adrenal tumors. Malignant (cancerous) tumors are very rare, occurring in two out of every one million people worldwide, and this cancer is more common in women than in men.

It is often difficult for a pathologist to distinguish between a benign and a malignant adrenal tumor. Several criteria are used to make a diagnosis, including the size and weight of the tumor, whether hormones are produced, and what hormones are produced. A benign tumor (**adenoma**) is usually less than 4–6 centimeters (1.57–2.3 inches) in diameter and likely causes changes in the blood level of only one hormone or may cause no changes at all. A malignant tumor is larger and may alter the level of several adrenal hormones. One reliable indicator for a malignant tumor is evidence that the cancer has spread (**metastasis**).

Types of cancers

Adrenal cortex

A disorder caused by an adrenal cortex tumor can occur alone, but often two or more conditions occur simultaneously. These disorders include

- **Cushing's syndrome**: a disorder resulting from prolonged exposure to high levels of cortisol. Most cases are the result of a pituitary gland dysfunction that causes excessive secretion of ACTH, but 20–25% are caused by a benign adrenal tumor, of which about 50% are malignant. Symptoms include obesity, moon-shaped face, increased fat in neck region, skin that bruises easily, severe **fatigue**, weak muscles, and high blood pressure. The common treatment is surgical removal of the affected gland. The outcome for a Cushing's syndrome patient with a benign adrenal adenoma is very good. Surgery usually results in a cure. The outcome is variable for malignant tumors.
- Aldosteronism (also called Conn's disease or hypoaldosteronism): a condition resulting from an abnormally high level of the hormone aldosterone. It is usually caused by an adenoma and rarely is the result of a malignant adrenal tumor. Symptoms include headaches, weakness, fatigue, high blood salt levels, frequent urination, high blood pressure, and an irregular heartbeat. An adenoma is usually removed surgically, although medication that controls the secretion of aldosterone is an effective treatment in many cases.
- Virilization syndrome (also called adrenal virilism or adrenogenital syndrome): a disorder caused by an excessive secretion of androgen hormones, leading to high levels of the male hormone **testosterone**. Adenomas that cause virilization are rare. When the condition accompanies Cushing's syndrome it may indicate an **adrenocortical carcinoma**. In males, the symptom is early onset of puberty, whereas in females symptoms include deepening of voice, a masculine build, and abnormal hairiness. The recommended treatment depends on the cause. If the condition is caused by an adenoma, use of medications that surpress ACTH secretion by the pituitary is the preferred treatment.
- Adrenocortical carcinoma: a rare cancer that is often not detected until it has spread to the liver or lung. The symptoms can include that of Cushing's syndrome, aldosteronism, virilization, or a combination of each of these conditions. The preferred treatment depends on the stage of the cancer, but usually involves surgery to remove the tumor, **chemotherapy**, and **radiation therapy**. If the cancer is caught at an early stage, the long-term survival can be good. If found at a later stage, about 30% of patients will survive five years after the initial diagnosis.

KEY TERMS

Adenoma—A benign tumor.

Inherited disorder—A disease that has a tendency to occur within a family. A disorder may be acquired because of a gene or genes that are passed from parent to child.

Pathologist—A doctor specializing in the identification of diseases by studying cells and tissues under a microscope.

Adrenal medulla

Only one type of tumor is associated with the adrenal medulla:

- Pheochromocytoma: a tumor that produces and secretes epinephrine and norepinephrine. Excessive secretion of these hormones can cause life-threatening hypertension and an irregular heartbeat. About 90% of these tumors are benign. Five percent of those diagnosed with this tumor have either **Von Hippel-Lindau syndrome**, type 2 of the **multiple endocrine neoplasia syndromes** (MEN), **Von Recklinghausen's neurofibromatosis**, or another inherited disorder. Symptoms include headaches, sweating, and chest pains. Treatment involves medication to control hypertension and the surgical removal of the affected gland. Long-term survival depends on early detection of the tumor and whether the tumor is benign or malignant.

See also Endocrine system tumors.

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ORGANIZATIONS

American Association of Clinical Endocrinologists. 1000 Riverside Avenue Suite 205, Jacksonville, FL 32204. 904-353-7878. <http://www.aace.com>.

National Adrenal Diseases Foundation. 505 Northern Boulevard, Great Neck, NY 11021. 516-487-4992. <http://www.medhelp.org/nadf>.

Monica McGee, M.S.

Adrenocortical carcinoma

Definition

Adrenocortical carcinoma is a malignant growth that originates in the cortex, or the outer portion, of one of the two adrenal glands.

Description

There are two adrenal glands in the body. Each one is paired with a kidney. The adrenal gland rests atop the kidney, on the side of the kidney that is nearest to the head.

An adrenal gland has two parts. The inner part (medulla) produces hormones such as epinephrine (adrenaline) that increases the heart rate. The cortex, or outer part, is made up of layers of epithelial cells, the cells that form coverings for the surfaces of the body. The cortex produces cortical hormones that are essential to well-being, or homeostasis.

The hormones produced by the cortex include glucocorticoids, mineralocorticoids, and sex hormones. Among the many hormones the cortex makes, three—aldosterone, cortisol and adrenal sex hormones— are very important. Aldosterone helps regulate salt and water content in the body. Cortisol helps keep sugars, fats and proteins in balance. Adrenal sex hormones influence sex organ development and sex drive (libido).

Adrenocortical carcinoma is a cancer that originates in the cortex of the adrenal gland. When a tumor grows in the adrenal cortex, it interferes with the production of hormones. Consequently, the effects of adrenocortical carcinoma can be severe and are almost always a threat to life.

There are two types of adrenocortical carcinoma. In one type, a tumor functions—that is, it makes hormones. In the other type, the tumor does not function. If the tumor functions, it acts like the cells in the cortex from which it grew and thus, produces hormones. But since it grows large, it produces extra amounts of hormones and the body is thrown far out of balance in any one of a number of ways.

When a tumor functions

How excess hormones cause the symptoms they produce is complex because more than one hormone from the adrenal cortex can be involved in producing a single symptom. For example, both aldosterone and cortisol, when present in extra quantities, may contribute to the increase in blood pressure (hypertension) many patients experience. Extra amounts of adrenal sex hormones can cause children to begin to display the sexual characteristics (hair growth, genital maturation) of adults. And adults with extra amounts of sex hormones often begin to display the sexual characteristics of the opposite sex. A woman may grow excess facial hair. A man may begin to develop fatty tissue in his breasts. Large quantities of adrenal sex hormones coursing through the body disrupt what would be a normal loop of feedback from the pituitary area of the brain. The pituitary is geared to send information, via a stimulating hormone, to the adrenal cortex, to prompt the tissue to manufacture adrenal sex hormone. When there is an extra amount of adrenal sex hormone in the body, the pituitary stops sending instructions to the adrenal cortex, as well as to other organs that produce the hormones responsible for male features. Thus, a man can begin to look like a woman because he does not have enough male hormones. A woman can begin to look like a man because she has too much adrenal sex hormone.

When a tumor does not function

If the tumor does not function, it just grows large, and may go unnoticed for a long time. Sometimes a tumor that does not function is called dormant. Often, the tumor that does not function first gets attention when it grows large enough to push against the body wall or an organ and cause pain; or when it has spread (metastasized) to another organ.

The adrenocortical carcinoma that does not function has a high likelihood of metastasizing before it is discovered. The two most common sites for metastases are the lungs and liver. Thus, even a non-functioning tumor may cause serious complications.

Demographics

Adrenocortical carcinoma is rare. Fewer than two in one million people, and perhaps as few as one in four million people, are diagnosed in a year. Two age groups are most likely to be diagnosed: those between zero and ten years of age, and those between 40 and 50 years.

Causes and symptoms

Causes

The cause of adrenocortical carcinoma is not known. Infection with bacteria or parasites is linked to other conditions of the adrenal glands, and there could be a connection with adrenocortical carcinoma. There is also evidence that adrenocortical carcinoma in children is caused by some chemical to which they were exposed as fetuses— possibly a chemical that the women carrying the children were exposed to in food, drink, or in the air.

Many tumors of the adrenal cortex have cells with extra copies of chromosomes, the beads of genetic material or DNA. Chemicals in the environment that are known to affect cells and cause mutations are being investigated as possible causes for adrenocortical carcinoma.

Symptoms

Depending on whether or not the tumor interferes with the production of hormones, the tumor may or may not be linked to symptoms during its early growth. A group of Japanese surgeons led by K. Kunieda reported the case of a 52-year-old man who had a tumor weighing more than two pounds at the time it was discovered. The tumor had not been producing extra hormones, and was not producing symptoms.

An adrenocortical tumor that functions produces many symptoms. Some of them are similar to those linked to other conditions, and many of these conditions have names that are based on a collection of symptoms and not on the cause. A combination of the following symptoms, known as **Cushing's syndrome**, could be caused by a tumor in the pituitary area of the brain, as well as by adrenocortical carcinoma:

- an abnormal accumulation of fatty pads in the face (creating the distinctive "moon face" of Cushing's syndrome); in the trunk (termed "truncal obesity"); and over the upper back and the back of the neck (giving the individual what has been called a "buffalo hump")
- purple and pink stretch marks across the abdomen and flanks
- high blood pressure
- weak, thinning bones (osteoporosis)
- muscle atrophy (due to protein loss)
- low energy
- thin, fragile skin, with a tendency toward both bruising and slow healing
- abnormalities in the processing of sugars (glucose), with occasional development of actual diabetes
- increased risk of infections
- irregular menstrual periods in women
- decreased sex drive in men and difficulty maintaining an erection
- abormal hair growth in women (in a male pattern, such as in the beard and mustache area), as well as loss of hair from the head (receding hair line)

Similarly, virilization syndrome, or the tendency of a child to exhibit adult sexual features, or a female adult to exhibit male features, can be caused by other conditions, such as tumors in the pituitary, or by adrenocortical carcinoma. So, too, with feminization, or the tendency of a male individual to exhibit female characteristics, such as enlarged breasts and fat deposits on the hips.

KEY TERMS

Biopsy—Tissue sample is taken from body for examination.

Carcinoma—A cancer that originates in cells that developed from epithelial tissue, a tissue found on skin and mucosal surfaces.

Computed tomography (CT)—X rays are aimed at slices of the body (by rotating equipment) and results are assembled with a computer to give a three-dimensional picture of a structure.

Homeostasis—Self-regulating mechanisms are working, body is in equilibrium, no uncontrolled cell growth.

Hormone—A chemical released by one organ of the body that affects the activity of another organ.

Inferior vena cava—The large vein that returns blood from the lower body to the heart.

Lymph nodes—Part of the lymphatic system, these clusters of tissue help to protect the body from foreign substances, organisms, and cancer cells.

Magnetic resonance imaging (MRI)—Magnetic fields used to provide images of the internal organs of the body.

Pituitary—A gland at the base of the brain that produces hormones.

Venography—Technique used for examining veins for blockage, using a dye to make the vein visible with scans similar to x ray.

Diagnosis

Symptoms usually cause a patient to talk with a physician. Blood and urine samples are examined to learn whether hormones are out of balance. Venography, a way of getting a picture of the inside of veins, is a technique that is still used to examine the adrenal glands prior to any decision about surgery. But the **magnetic resonance imaging** (MRI) scan has replaced venography in many facilities. **Computed tomography** (CT) scan is also used to examine the adrenal cortex.

Treatment team

Depending on symptoms, the first specialized physician an individual consults may either be an endocrinolo-

gist (a physician who focuses on hormones) or a urologist (a physician who focuses on the study of the kidneys and nearby structures). Either one of them, or a medical oncologist (a physician who focuses on treating patients with cancer) will lead the treatment team. A surgeon will be on the team too because in almost all cases removal of the adrenocortical carcinoma to the fullest extent possible is standard procedure.

Nurses will be on the team to help with administering drugs and monitoring the status of the patient. And if the patient is given **chemotherapy**, technicians skilled in the treatment will be part of the team.

Clinical staging, treatments, and prognosis

Adrenocortical tumors are assigned to one of four stages.

- Stage I tumors have not spread beyond the cortex of the adrenal gland and are less than two in (5 cm) in their greatest dimension.
- Stage II tumors have not spread beyond the cortex of the adrenal gland and are more than two inches.
- Stage III tumors have either spread into tissues around the adrenal cortex or they have spread into lymph nodes near the adrenal glands, or both.
- Stage IV tumors have spread to lymph nodes and other organs near the adrenal cortex or to other organs of the body.

A plan for treatment is based on the size and extent of the tumor. Surgical removal of the tumor, radiation and chemotherapy are all used. Method of treatment depends on how large the carcinoma is and whether it has spread to other organs. In some cases the treatment is strictly palliative (provides comfort) and is not expected to halt the course of the cancer. Palliative treatment can include surgery to reduce the size of the tumor, as well the pain a large tumor causes by pushing against other organs.

Because adrenocortical carcinoma that metastasizes often moves into the renal (kidney) vein and then, the inferior vena cava, venography or MRI scan prior to surgical removal of all or part of the tumor is important. If the tumor has grown into a vein, a piece of it can be dislodged and become a dangerous object. The piece of tumor begins to move in the blood flow and it is capable of getting stuck in a small blood vessel in the heart or the brain, and causing a stroke.

The drug **mitotane** gives some good results is slowing tumor growth in certain patients. But the only therapy that provides relief in most patients is the removal of the tumor.

QUESTIONS TO ASK THE DOCTOR

- In which stage is the carcinoma?
- With this type of carcinoma, what is the five-year survival rate for a person of my age and gender? What is the one-year survival rate?
- Is there a center that specializes in treating this type of cancer?
- Are there any clinical trials in which I might be eligible to participate?
- Does this health care institution have a support group for individuals with my type of carcinoma?
- What is your approach to relieving pain? (Do we agree?)

The outlook for individuals with adrenocortical carcinoma depends on the stage of the cancer. Because seven in ten individuals are diagnosed only after the cancer has reached stage III or stage IV the five-year survival rate for all stages is 40%. And for individuals with stage IV carcinoma it is much less, with most patients dying within nine months of diagnosis.

Alternative and complementary therapies

Yoga, biofeedback or other relaxation techniques may help manage pain.

Coping with cancer treatment

Being an active member of the treatment team is important. Premier cancer centers encourage patients to play such a role. A support group can also help.

Clinical trials

The Cancer Information Service at the National Institutes of Health, Bethesda, Md., offers information about **clinical trials** that are looking for volunteers. The Service offers a toll-free number at 1-800-422-6237.

Prevention

No prevention is known.

Special concerns

The excess production of hormones that indicate functioning tumors in adrenocortical carcinoma can also be symptoms of other conditions. A tumor in the

pituitary gland can cause the pituitary to produce too much of the hormone that stimulates the adrenal cortex to make cortical hormones. The symptoms are identical to those for the adrenocortical tumor. A pituitary tumor must sometimes be ruled out when an adrenocortical carcinoma is suspected. Brain scans may be necessary.

Resources

PERIODICALS

Kunieda, K., et al. "Recurrence of giant adrenocortical carcinoma in the contralateral adrenal gland 6 years after surgery." *Surgery Today* 30 (March 2000): 294-7.

Wajchenber, B. L., et al. "Adrenocortical carcinoma: clinical and laboratory observations." *Cancer* 88 (February 15, 2000): 711-36.

Diane M. Calabrese

Advance directives

Definition

An advance directive is a written document in which people clearly specify how medical decisions affecting them are to be made if they are unable to make them, or to authorize a specific person to make such decisions for them.

Description

Advance directives are recognized in most industrialized countries of the world. In the United States, by law, the creation of an advance directive is the right of all competent adults. The goal of this legislation is to empower all health care consumers to make their own judgments regarding medical decision-making, to approve of potential treatment they believe they would want, and to refuse care they do not perceive as being in their best interest. These directives are generally divided into living wills or durable powers of attorney.

Federal law requires that all health care providers (health maintenance organizations, or HMOs, skilled nursing care facilities, hospices, home health care providers, and hospitals) make information regarding advance directives available to all people in their care. Many states require that two people witness such advance directives.

Living wills

Living wills go into effect while the individual is still living, but is unable to communicate his/her wishes regarding care. Traditionally, a living will has specified the individual's wishes concerning procedures that would sustain life if he/she were terminally ill. Newer advance directives do not limit such preferences to terminal illness but instead go into effect whenever the individual is unable to speak for him/herself.

There are several ways of preparing a living will. Sometimes a preprinted form is provided, or people may create their own form, or may simply write down their wishes. Though all 50 states and the District of Columbia recognize the validity of advance directives, each state's laws have differences as to whether one or all of these types of preparation of the document are legal and binding in that state. It is recommended that people speak to their attorney or physician to ensure that their wishes are carried out.

Durable power of attorney for health care

A durable power of attorney for health care is the second type of advance directive. This is a signed, dated, and witnessed document that authorizes a designated person (usually a family member or close friend) to act as an agent, or proxy. This empowers the proxy to make medical decisions for a person when the person is deemed unable to make these decisions him/herself. Such a power of attorney frequently includes the person's stated preferences in regard to treatment. Several states do not allow any of the following people to act as a person's proxy:

- the person's physician, or other health care provider
- the staff of health care facilities that is providing the person's care
- guardians (often called conservators) of the person's financial affairs
- employees of federal agencies financially responsible for a person's care
- any person that serves as agent or proxy for 10 people or more As in the case of living wills, regulations regarding such powers of attorney vary from state to state. Some states provide printed forms, and require witnesses, while other states do not.

Causes

As medical advances provide greater than ever means of extending life, it becomes increasingly important for people to evaluate which of the available means they would wish used. If this is not done, people run the

KEY TERMS

Competent—Duly qualified; having sufficient ability or authority; possessing all the requirements of law.

Dialysis—A technique used to remove waste products from the blood and excess fluid from the body as a treatment for kidney failure.

Hyperalimentation—The administration of a nutrient solution into a large, central vein near the heart. It is often used supplementary to eating, but can provide complete nourishment.

Tube feeding—Administration of nourishment, in nutritionally complete solutions, via tube into the stomach or intestines. Tubes can be either nasogastric, or inserted through the nose into the stomach via the esophagus, or surgically implanted directly into the stomach. These are usually used to sustain life when a person is unable to eat or take fluids by mouth.

QUESTIONS TO ASK THE DOCTOR

- What is the prognosis for my type of cancer?
- What are the possible treatments?
- What are the side effects of these treatments?
- What are the laws in my state regarding living wills and durable powers of attorney for health care?
- How can I ensure that my wishes will be carried out regarding advance directives?

risk of having health care providers make critical decisions regarding their care. The absence of advance directive information can also create dilemmas and increased stress for loved ones. Some of the terms describing now-routine medical interventions that can maintain life under dire circumstances include:

- cardiopulmonary resuscitation (CPR), the use of chest compressions and/or mouth-to-mouth resuscitation to restart heart beat and/or respirations
- ventilators or respirators that physically deliver oxygen via a tube into the windpipe when the lungs are unable to work on their own
- Life-sustaining care encompasses the use of machinery or equipment that prolongs life by keeping the body functioning. Examples of life-sustaining care include hyperalimentation, tube feedings, and kidney dialysis.

In contrast, life-enhancing care, sometimes referred to as Care and Comfort Only, involves the provision of high quality, but non-heroic medical care until death occurs naturally. Important examples of life-enhancing care include administration and monitoring of medications, carrying out other measures to control pain, comfort measures such as bathing and massage, and offering food and fluids.

Special concerns

Though specifics vary, all states have laws allowing people to spell out their health care wishes for a time when they might be unable to speak for themselves. But, as noted, there is a potential for disparity in how advance directives are interpreted. In most hospitals, an ethics committee is available to assist and support both patients and families faced with decisions regarding medical care. In 1995, the American Association of Retired Persons (AARP), with the help of the American Bar Association (ABA) and the American Medical Association (AMA), produced a combined living will and power of attorney for health care document that provides very specific and detailed statements of a person's wishes. Further information regarding the laws in individual states can be obtained from the AARP, ABA, or AMA.

The AARP recommends that those individuals considering making an advance directive address the following issues:

- What the person's goals for medical treatment are: Should treatment be used to sustain life, regardless of the quality of that life?
- Who should act as the person's proxy or agent? It is important for the person making an advance directive to actually speak with this designated person and make his/her wishes known.
- Though there is no formula for specificity, the AARP recommends that instructions be made as clear and specific as possible, but should not restrict the proxy from making informed decisions at the time that cannot be anticipated in advance.
- To ensure that an advance directive is carried out, copies of it should be given to a person's physician, proxy, family, or any other interested party.

Resources

ORGANIZATIONS

American Association of Retired Persons Legal Counsel for the Elderly., P.O. Box 96474, Washington, DC, 20090-6474.

American Bar Association. <http://www.abanet.org>.

American Medical Association. <http://www.ama-assn.org>.

Center for Healthy Aging. <http://www.careproject.net>.

Choices In Dying, Inc., 200 Varick Street, New York, New York 10014-4810. (800) 989-WILL.

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AIDS-related cancers

Definition

The AIDS-related cancers are a group of cancers that occur more frequently in persons with human immunodeficiency virus (HIV) infection than in the general population. The most common form of AIDS-related cancer, **Kaposi's sarcoma** (KS), was one of the first indications of the AIDS epidemic in the early 1980s. New cases of KS and AIDS-related lymphomas increased until about 1996. The decline started a few years earlier when HIV infection rates slowed, but cases of these cancers began to decrease more with the introduction of effective antiretroviral therapies.

Description

In order to understand the causes and treatment of AIDS-related cancers, it is useful to begin with a basic description of HIV infection. AIDS, or acquired immunodeficiency syndrome, is a disease of the immune system that is caused by HIV. HIV is a retrovirus, a single-stranded virus containing ribonucleic acid (RNA) and an enzyme called reverse transcriptase. This enzyme enables the retrovirus to make its genetic material part of the DNA in the cells that it invades. HIV selectively infects and destroys certain subtypes of white blood cells called CD4 cells, which are an important part of the body's immune system. As an infected person's number of CD4 cells drops, he or she is at risk of developing opportunistic infections, disorders of the nervous system, or an AIDS-related cancer. HIV is transmitted through blood or blood products that enter the bloodstream—most commonly through sexual contact or contaminated hypodermic needles.

Kaposi's sarcoma

Kaposi's sarcoma is the most common type of cancer related to HIV infection. About 20% of patients diagnosed with AIDS will eventually develop KS. There are two other major subtypes of KS—so-called classic KS and African KS—with different causes that are not yet well understood. AIDS-related KS (also called epidemic KS) is characterized by purplish or brownish lesions (areas of diseased or injured tissue) on the skin, in the mouth, or in the internal organs. The lesions may take the form of small patches or lumps (nodular lesions), large patches that grow downward under the skin (infiltrating lesions), or lumpy swellings in the lymph nodes. Unlike other cancers that typically develop in one organ or area of the body, KS often appears simultaneously in many different parts of the body. It may be the first indication that the patient has AIDS.

Non-Hodgkin's lymphoma

Lymphomas are cancers of the immune system that develop when white blood cells called lymphocytes begin to grow and multiply abnormally. The increased numbers of lymphocytes cause the lymph nodes, the organs that produce these white blood cells, to swell and form large lumps that can be felt. Lymphomas are divided into two large categories: those that are related to **Hodgkin's disease** (HD), and non-Hodgkin's lymphoma (NHL). HD can be differentiated from NHL by the presence of Reed-Sternberg cells in the lymphatic tissue; these cells are not found in any other type of cancer.

NHL occurs more often than Hodgkin's disease; about 50,000 new cases are diagnosed annually in the United States. They may involve the spleen, liver, bone marrow, or digestive tract as well as the lymph nodes. Three important types of NHL are related to AIDS:

- Primary central nervous system lymphomas (PCNSL). This type accounts for about 20% of NHL cancers found in AIDS patients, but only 1% to 2% of NHL cancers in patients not infected by HIV. Lymphomas of this type start in the brain or the spinal cord. Symptoms include headaches, paralysis, seizures, and changes in the patient's mental condition. Patients diagnosed with PCNSL are more likely to suffer from advanced HIV infection than patients with other types of NHL.
- Systemic lymphomas. These also are called peripheral lymphomas. They begin in the lymph nodes or other parts of the lymphatic system and may spread throughout the body. **Burkitt's lymphoma** (BL) is a type of systemic lymphoma that is 1,000 times more common in AIDS patients than in the general population.
- Primary effusion lymphomas, also called body cavity-based lymphomas (BCBL). This type of NHL is relatively rare, but seems to be related to infection by human herpesvirus 8 (HHV-8) in addition to HIV.

Cervical and anal cancers

In women, cancer of the cervix (the lower end of the uterus or womb) is more likely to occur in HIV-infected individuals than in the general female population. About 60% of women with HIV infection are found to have some kind of abnormal tissue growth or cell formation in the cervix when a **Pap test** is performed. The **human papilloma virus** (HPV) is thought to be a co-factor in the development of cervical cancers. Papilloma viruses are a group of tumor-causing viruses that also cause genital warts. Cervical cancers develop more rapidly in HIV-positive than in HIV-negative women, are harder to cure, and are more likely to recur.

Cancers of the anus represent less than 1% to 2% of cancers of the large bowel. There are about 10,000 cases of **anal cancer** annually in the United States. The high rates of occurrence of this type of cancer in gay men may be related more closely to the presence of HPV and to the practice of anal intercourse than to HIV infection by itself.

Other AIDS-associated cancers

Other cancers linked to HIV infection include **testicular cancer**, cancers of the mouth, and a type of cancer of the bone marrow called **multiple myeloma**. Some other cancers, including **breast cancer**, lung cancer, and **melanoma** (a type of skin cancer), are thought to occur more frequently among people with AIDS even though they are not identified as AIDS-associated cancers in the strict sense.

At a 2004 conference, presenters noted that incidence of five cancers had risen since introduction of new antiretroviral therapies to treat HIV. In Chicago, patients treated with highly active antiretroviral therapy (HAART) had higher incidence of lung cancer, head and neck cancer, Hodgkin's lymphoma, melanoma and anorectal cancer than control groups.

Demographics

The demographic distribution of AIDS-related cancers varies somewhat depending on the type of cancer. Epidemic KS is about 10 times more common among gay men than among members of other groups at risk for AIDS (hemophiliacs, intravenous drug users, etc.); it affects men eight times as frequently as women. AIDS-related Hodgkin's disease occurs more frequently among intravenous drug users. By contrast, AIDS-related lymphomas occur with equal frequency in members of all risk groups—including the children of persons with HIV infection.

Causes

The most common types of AIDS-related cancers have been linked to oncogenic (tumor-causing) viruses:

- Human herpesvirus 8 (HHV-8) is associated with KS and some of the less common types of AIDS-related lymphomas (ie. cancers of the lymphatic system).
- **Epstein-Barr virus** (EBV) is associated with the more common types of AIDS-related lymphomas, particularly PCNSL and Burkitt's lymphoma.
- Human papillomavirus (HPV) is associated with anal cancer and with **cervical cancer** in women.

Oncogenic viruses cause cancer by changing the genetic material inside tissue cells. When this genetic material is changed, the cells begin to grow and multiply uncontrollably. The abnormal tissue formed by this uncontrolled growth is called a tumor. A healthy human immune system has a greater ability to protect the body against oncogenic viruses and to stop or slow down tumor formation. Since the retrovirus that causes AIDS weakens the immune system, persons with AIDS are at greater risk of developing cancers caused by oncogenic viruses.

Some types of AIDS-related cancers, such as Burkitt's lymphoma, have been linked to changes in human chromosomes (translocations). In a translocation, a gene or group of genes moves from one chromosome to another. Burkitt's lymphoma is associated with exchanges of genetic material between chromosomes 8 and 14 or between chromosomes 2 and 22.

Special concerns

An important special concern for patients with AIDS-related cancers is the difficulty of combining cancer treatment—especially chemotherapy—with treatment for HIV infection. Since 1996, HAART has been the standard treatment for AIDS. HAART is a combination drug therapy involving three or four different medications. Because of the powerful side effects of these drugs, patients with AIDS-related cancers are usually put on low-dose **chemotherapy** for the cancer. The chemotherapy, however, increases the patient's risk of developing an AIDS-related infection, such as **thrush** or *Pneumocystis carinii* **pneumonia** (PCP).

Another special concern for patients with AIDS-related cancers is fear of rejection by friends and loved ones. Although the moral stigma attached to HIV infection is not as strong as it was at the beginning of the epidemic, some patients may still fear condemnation by others. Most hospitals have chaplains or spiritual

counselors who can help patients with these concerns or put them in touch with someone from their own spiritual tradition.

Treatments

The different types of AIDS-related cancers have different treatment considerations.

Kaposi's sarcoma

KS differs from other solid tumors in that it lacks a stage or site of origin in which it can be cured. In addition, there is no relationship between the stage of KS and its response to treatment. Many doctors treat early KS with chemotherapy injections or treat localized lesions with **radiation therapy** rather than give the patient systemic chemotherapy. In 1999, the FDA approved alitretinoin (Panretin) gel as a topical treatment for KS. When systemic chemotherapy is used, the standard regimens are a combination of **vinblastine** (Velban) and **vincristine** (Oncovin) on a weekly schedule, or a combination of **doxorubicin**, **bleomycin**, and vincristine given every week. Surgery is not often used in the treatment of KS.

Non-Hodgkin's lymphoma

Patients with early, slow-growing forms of NHL are usually treated with radiation. The later stages of slow-growing **non-Hodgkin's lymphomas** may be treated with chemotherapy (single-agent or combination), or with a combination of radiation and chemotherapy. Common treatments for more aggressive AIDS-related lymphomas are the combination chemotherapy regimens known as CHOP (**cyclophosphamide**, doxorubicin, vincristine, and prednisone) or m-BACOD (intermediate-dose **methotrexate**, bleomycin, doxorubicin, cyclophosphamide, vincristine, and **dexamethasone**). In general, AIDS-related lymphomas are more aggressive than non-HIV-related lymphomas and do not respond as well to chemotherapy. PCNSL is usually treated with radiation therapy alone because most chemotherapy drugs cannot cross the blood-brain barrier and enter the central nervous system.

Newer forms of treatment for non-Hodgkin's lymphomas include bone marrow and stem cell transplants and immunotherapy with the use of **monoclonal antibodies** (MABs). MABs are antibodies produced by cloned mouse cells grown in a laboratory. They target cancer cells and bind to them, alerting cells of the immune system to destroy the abnormal cells. MABs are sometimes given together with chemotherapy. Use of HAART to treat HIV patients also increases survival of patients with AIDS-related Hodgkin's lymphomas.

Cervical and anal cancers

Cervical and anal cancers are treated in the early stages with a combination of surgery and radiation. Larger or later-stage tumors are treated with chemotherapy (mitomycin or **cisplatin** and **fluorouracil**) in addition to surgery and radiation treatment.

Alternative and complementary therapies

In the early years of the AIDS epidemic, a variety of alternative approaches were used to treat the internal forms of KS as well as the external skin lesions: homeopathic preparations of periwinkle, poke root (phytolacca), and mistletoe; a mixture of selenium, aloe vera gel, and silica; Chinese patent medicines; periodic three- to seven-day grape fasts as part of an overall vegetarian diet; and castor oil packs.

The only alternative treatment for KS that has been evaluated by the National Institutes of Health (NIH) is shark cartilage. Shark cartilage products are widely available in the United States as over-the-counter (OTC) preparations. The use of shark cartilage to treat KS derives from a popular belief that sharks and other cartilaginous fish (skates and rays) do not get cancer. This therapy, however, has not been proven to be effective.

Other alternative treatments for AIDS-related KS include:

- Naturopathic remedies. High doses of vitamin C, zinc, echinacea, or goldenseal to improve immune function; or preparations of astragalis, osha root, or licorice to suppress the HIV virus.
- Homeopathic remedies. These include a homeopathic preparation of **cyclosporine** and another made from a dilution of killed typhoid virus.
- Ozone therapy.

With regard to other categories of AIDS-related cancers, there have been reports of using hydrazine sulfate or laetrile to treat AIDS-related lymphomas. Some researchers in Germany are investigating mistletoe extracts as a treatment for AIDS-related cancers in women.

Complementary therapies are used in the treatment of AIDS-related cancers to help patients keep up their will to live; to cope with such side effects as **depression**, nausea caused by chemotherapy, concerns about disfigurement, and fear of rejection; and to gain comfort from supportive social groups. Specific complementary approaches that have been recommended for cancer patients include acupuncture, creative visualization, pet therapy, meditation, prayer, yoga, Reiki, aromatherapy, and some herbal remedies (St. John's wort for depression, peppermint or spearmint tea for nausea).

KEY TERMS

Blood-brain barrier—A layer of tightly packed cells in the small blood vessels in the brain that prevent many medications and other substances from entering the brain.

Burkitt's lymphoma—A subtype of non-Hodgkin's lymphoma that is one thousand times more common in AIDS patients than in the general population.

Highly active antiretroviral therapy (HAART)—A combination drug therapy for AIDS, usually consisting of three or more medications.

Human herpesvirus (HHV)—A family of viruses that contain DNA and cause a number of diseases, including chickenpox, shingles, and genital herpes.

Human papilloma virus (HPV)—A type of tumor-causing virus that causes genital warts and is associated with AIDS-related cervical cancers in women.

Kaposi's sarcoma (KS)—The most common type of AIDS-related cancer. KS is characterized by purplish or brownish spots on the skin and may spread to the internal organs.

Lymphatic system—The system of glands, tissues, and vessels in the body that produces lymphocytes and circulates them through the body in a clear, yellowish fluid called lymph.

Lymphocyte—A type of white blood cell involved in the production of antibodies.

Non-Hodgkins lymphoma (NHL)—A type of cancer of the immune system that is the second most common form of AIDS-related cancer. It is sometimes called AIDS-related lymphoma.

Oncogenic—Producing or causing tumors. The most common types of AIDS-related cancers are associated with oncogenic viruses.

Monoclonal antibody—An antibody produced in the laboratory from a cloned cell rather than in the body.

Retrovirus—A virus that contains a single strand of RNA and a unique enzyme called reverse transcriptase.

Translocation—The movement of a gene or group of genes from one chromosome to another.

Clinical trials

Thirty-nine **clinical trials** of treatments for AIDS-related lymphomas, 13 trials of treatment for KS, and 13 trials of treatments for PCNSL were being conducted in the United States. **Thalidomide**, a drug that made headlines in the 1960s for its role in causing birth defects, was shown to be effective in treating KS in July 2000. It is undergoing further study.

See also Immunologic therapies.

Resources

BOOKS

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Eltom, Mohamed A., et al. "Trends in Kaposi's Sarcoma and non-Hodgkin's Lymphoma Incidence in the United States from 1973 through 1998." *Journal of the National Cancer Institute* August 21, 2002:1204–1207.

"HAART Increases Survival of Patients with HIV-associated Hodgkin Disease." *Immunotherapy Weekly* August 4, 2004: 71.

San Francisco AIDS Foundation. *Bulletin of Experimental Treatments for AIDS*

ORGANIZATIONS

AIDS Clinical Trials Group (ACTG). c/o William Duncan, PhD, National Institutes of Health. 6003 Executive Boulevard, Room 2A07, Bethesda, MD 20892.

American Cancer Society (ACS). 1599 Clifton Road, NE, Atlanta, GA 30329. (404) 320-3333 or (800) ACS-2345. Fax: (404) 329-7530. <http://www.cancer.org>.

National Cancer Institute, Office of Cancer Communications. 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. TTY: (800) 332-8615. <http://www.nci.nih.gov>.

National Institutes of Health National Center for Complementary and Alternative Medicine (NCCAM) Clearinghouse. PO Box 8218, Silver Spring, MD 20907-8218. (888) 644-6226. TTY/TDY: (888) 644-6226. Fax: (301) 495-4957. <http://nccam.nih.gov>.

San Francisco AIDS Foundation (SFAF). 995 Market Street, #200, San Francisco, CA 94103. (415) 487-3000 or (800) 367-AIDS. Fax: (415) 487-3009. <http://www.sfaf.org>.

OTHER

The Body: An AIDS and HIV Information Resource. <http://www.thebody.com>.
<http://www.hivchannel.com>.
<http://www.oncologychannel.com>.

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AJCC *see* **American Joint Commission on Cancer**

Alcohol consumption

Description

Alcohol (ethyl alcohol or ethanol) consumption has a social aspect to it, but it is often abused. The effect of alcohol consumption on the body depends on how often it is consumed, how much, and the alcohol content of the drinks. Frequent alcohol use may encourage alcohol dependence or alcoholism. Alcoholism is a chronic disease that progresses and is often fatal. It is a primary disorder and not only a symptom of other diseases or emotional disorders. Factors such as psychology, culture, genetics, and response to physical pain influence the severity of alcoholism.

Special concerns

Health concerns relating to alcohol consumption

Alcoholic liver disease may occur with chronic alcohol consumption. This disease is manifested in three forms: steatosis (fatty liver), alcoholic hepatitis, and cirrhosis. Alcohol abuse is responsible for 60% to 75% of cases of cirrhosis, which is a major risk factor for eventually developing primary liver cancer. Alcohol may further compromise the health of an individual through:

- Immune system suppression. People with alcoholism are prone to infections, in particular, pneumonia.
- Gastrointestinal problems; especially **diarrhea** and hemorrhoids.
- Mental and neurological disorders. Chronic use eventually leads to **depression** and confusion. In severe cases, gray matter in the brain is destroyed, possibly leading to psychosis and mental disturbances.
- Alcoholism increases levels of the female hormone estrogen and reduces levels of the male hormone **testosterone**, factors that contribute to impotence in men.
- Hypoglycemia (a drop in blood sugar) is particularly dangerous for diabetics taking insulin.
- Severe alcoholism is associated with osteoporosis.
- Drug interactions.

Alcohol's association with cancer

Alcohol consumption is an important risk factor for many types of cancer including cancer of the: pharynx, larynx, mouth, breast, liver, lung, esophagus, gastric, pancreatic, urinary tract, prostate, and brain. It also increases risk for ovarian and colorectal cancer, **lymphoma**, and leukemia.

The risk of **breast cancer** and other cancers rises as alcohol consumption increases. Approximately 75% of cancers of the esophagus and 50% of cancers of the mouth, throat, and larynx are due to alcoholism. Other research has demonstrated, however, that wine poses less danger for these cancers than beer or hard liquor. Alcohol, when combined with smoking, increases the chances of developing mouth, throat, pharynx, larynx and esophageal cancers significantly. For **esophageal cancer**, there is a 3 to 8 fold increase in risk for those who drink 40-100 grams of alcohol per day, and the risks are even greater when smoking is added. A 2004 study reported that moderate wine consumption might have protective effects against formation of precancerous polyps in the colon, but that people who drank heavily had a much higher risk of developing colorectal cancer.

Research has shown that women who consume only one alcoholic drink per day have a 30% higher risk of dying from breast cancer than nondrinkers. Even consuming small amounts of alcohol may increase breast cancer risk, particularly in postmenopausal women due to increased hormone levels circulating in the blood.

Cancer patients may find that alcohol consumption interferes with the effectiveness of anticancer therapy and may cause them to become even sicker.

Nutritional impact of alcohol consumption

Even moderate alcohol consumption can have detrimental effects on the health of cancer patients. If food intake is replaced by alcohol to a large extent, malnutrition is likely to occur. In fact, alcoholism is a major cause of malnutrition. The body requires protein, carbohydrate, fat, **vitamins**, and minerals, but these often are inadequate with heavy alcohol consumption. Nutritional

status is thus further compromised in cancer patients who abuse alcohol.

Like food, alcohol contains energy, or calories. But alcohol does not contain many of the nutrients required by the body. Furthermore, because few nutrients are provided in alcohol, the vitamin and mineral content of the diet may be poor, even if the total energy intake is adequate. Alcohol contains approximately 7 kilocalories (Kcal) per gram, while carbohydrate or protein contain about 4 Kcal per gram. Thus, the nutrients required by the body will not be obtained if alcohol replaces food intake to some extent. In fact, alcohol interferes with the body's mechanisms that regulate food intake, and therefore food intake decreases. When inadequate nutrients are consumed, the body may become weaker and less able to tolerate cancer therapies. As nutritional status declines, it becomes more difficult to fight off illness and infection. In addition, the toxic effects of ethanol interfere with the absorption, metabolism, and storage of nutrients that are provided in foods. Several organs can be damaged in this process, primarily the liver and brain, but also the cardiovascular, endocrine, immune, and hematopoietic systems.

Alcohol may further compromise nutritional status of an individual through:

- malabsorption of vitamins and minerals, particularly folate, thiamine, Vitamins B6 and B12, calcium, magnesium, and fat-soluble vitamins (A, E, and K)
- inducing early satiation
- reduced absorption of amino acids (the building blocks of protein)
- immune suppression
- respiratory disorders
- liver, gastrointestinal tract, and pancreas damage

Dietary interactions relating to cancer

Alcohol has numerous influences on the nutritional status of the cancer patient which often already is compromised by the disease. Cancer often increases the body's energy (calorie) and protein requirements. These increased needs may be due to the effects of the tumor or the effects of treatment (surgery, radiation, or **chemotherapy**). At the same time, cancer patients tend to decrease their food intake, often due to **anorexia**, which can be characterized as a loss of interest in eating. Anorexia, cachexia, and **weight loss** are common side effects of certain cancers and cancer therapies, so a cancer patient who consumes alcohol should be careful not to replace needed energy and nutrients with too many calories from alcohol.

KEY TERMS

Alcoholism—A primary disorder and chronic disease, progressive and often fatal where an individual is dependent on alcohol.

Anorexia—A condition frequently observed in cancer patients characterized by a loss of appetite or desire to eat.

Larynx—The enlarged upper end of the trachea below the root of the tongue and the primary organ that enables speech.

Pharynx—The passageway for air from the nasal cavity to the larynx and food from the mouth to the esophagus, also providing a place for resonance.

Satiation—A feeling of fullness or satisfaction during or after food intake.

Recommendations regarding alcohol consumption

Although moderate alcohol consumption is recommended to reduce the risk of heart disease, other lifestyle factors such as a healthy diet and exercise reduce the risk of heart disease and cancer.

The American Cancer Society's (ACS) *Guidelines on Diet, Nutrition, and Cancer Prevention* recommend moderation in alcohol intake. Experts suggest that intake should be limited to no more than an average of two drinks daily for women and three drinks a day for men. Research from Denmark in 2004 reported that increased alcohol consumption in a woman's 50s also increased her risk for breast cancer.

Treatments

Two of the most common forms of treatment for alcoholics are cognitive-behavioral and interactional group psychotherapy based on the Alcoholics Anonymous 12-step program. People with mild to moderate withdrawal symptoms are usually treated in outpatient programs through counseling, and/or support groups. Individuals may be treated in a general or psychiatric hospitals or substance abuse rehabilitation facility if they: possess coexisting medical or psychiatric disorders; have a difficult home environment; are a danger to themselves or others; have not responded to other conservative treatments. Inpatient programs often include physical and psychiatric development, detoxification, psychotherapy or cognitive-behavioral therapy, and an introduction to Alcoholics Anonymous.

Resources

PERIODICALS

"Heavy Alcohol Consumption Linked to CRC." *Patient Care* January 2004: 8–10.

"Lifelong Alchohol Consumption Unrelated to Postmenopausal Breast Cancer Risk." *Cancer Weekly* March 16, 2004: 31.

Crystal Heather Kaczkowski, M.S.
Teresa G. Odle

Aldesleukin

Definition

Aldesleukin is interleukin, or specific kind of biological response modifier, that is used to treat metastatic renal cell carcinoma (a form of kidney cancer) and metastatic **melanoma**. Aldesleukin is also known as interleukin-2, IL-2 and the trademarked name Proleukin.

Purpose

When renal cell carcinoma and metastatic melanoma (cancer of the skin that arises in the pigmented cells of the skin or eyes) do not respond to other therapies, they are candidates for treatment with aldesleukin.

Description

Aldesleukin is a biological response modifier (BMR). It promotes the development of T cells, or the cells in the lymphatic system that can fight cancer cells in cell-to-cell interaction. The human body produces aldesleukin naturally.

For use in therapy, aldesleukin is manufactured in a laboratory setting, using biotechnology methods, or methods that combine biological mechanisms and tools from technology. In the instance of aldesleukin, the compound is made in large quantities by using recombinant DNA technology. The DNA, or hereditary material, that provides instructions for making aldesleukin, is put in bacterial cells under laboratory confinement. The cells then produce large quantities of the human compound that are harvested, purified, and used for treatment.

Treatment with aldesleukin is considered palliative, which means it provides comfort but does not produce a cure. In some cases, aldesleukin is used together with an anticancer drug.

KEY TERMS

Corticosteroids—Compounds that are made naturally by the body in the cortex of the adrenal glands and that are also made synthetically, or in the laboratory.

Intravenous line—A tube that is inserted directly into a vein to carry medicine directly to the blood stream, bypassing the stomach and other digestive organs that might alter the medicine.

Kilogram—Metric measure that equals 2.2 pounds.

Lymphatic system—The system that collects and returns fluid in tissues to the blood vessels and produces defensive agents for fighting infection and invasion by foreign bodies.

Metastatic—Spreading from one part of the body to another.

Milligram—One-thousandth of a gram, and there are one thousand grams in a kilogram. A gram is the metric measure that equals about 0.035 ounces.

Toxicity—The quality of acting as a poison.

T cell—A cell in the lymphatic system that contributes to immunity by attacking foreign bodies, such as bacteria and viruses, directly.

Recommended dosage

Standard treatment with aldesleukin is via an intravenous line. The standard dose is 0.037 milligrams per kilogram of body weight every eight hours. For renal cancer, up to 15 doses can be repeated over 7-10 days every 5–6 weeks. But because the aldesleukin has such severe side effects, lower doses are being tried. And delivery of aldesleukin via an inhaler, or a mechanical device that puts the compound into the air passages when a person breathes, is being used in the case of metastatic melanoma that has invaded the lungs.

Precautions

Side effects from aldesleukin are generally very severe. No one who already has a metastatic growth in the central nervous system should take the treatment because aldesleukin will incite, or aggravate, symptoms from the tumor.

Side effects

Aldesleukin causes changes in the ways body fluids accumulate in the body that can lead to **ascites** and pleu-

ral effusions. Changes in personality are common due to the influence the drug has on the central nervous system. Among the most severe side effects is the possibility a patient will slip into a coma, or unconscious state. Other side effects may include alterations in liver function, skin reactions, such as rash, and infections may be severe and life threatening. Less serious, and almost always transient side effects, include flu-like symptoms, such as **nausea and vomiting**.

Interactions

Aldesleukin interacts with drugs that affect the central nervous system and it should not be taken with drugs that are used to modify moods or disposition (psychotropic agents). Many drugs, including those used to control blood pressure, heart beat and kidney function, increase the toxicity of aldesleukin and should not be taken in combination with it. **Corticosteroids** also interfere with the action of aldesleukin.

Physicians must be informed about every drug a patient is taking so interactions can be avoided.

Diane M. Calabrese

Alemtuzumab

Definition

Alemtuzumab is sold as Campath in the United States. Alemtuzumab is a humanized monoclonal antibody that selectively binds to CD52 (a protein found on the surface of normal and malignant B and T cells) that is used to reduce the numbers of circulating malignant cells of patients who have B-cell **chronic lymphocytic leukemia** (B-CLL).

Purpose

Alemtuzumab is a monoclonal antibody used to treat B-CLL, one of the most prevalent forms of adult **chronic leukemia**. It specifically binds CD52, a protein found on the surface of essentially all B and T cells of the immune system. By binding the CD52 protein on the malignant B cells, the antibody targets it for removal from the circulation. Scientists believe that alemtuzumab triggers antibody-mediated lysis of the B cells, a method that the immune system uses to eliminate foreign cells.

Alemtuzumab has been approved by the FDA for treatment of refractory B-CLL. For a patient's disease to be classified as refractory, both alkylating agents and **fludarabine** treatment must have been tried and failed. Thus, this drug gives patients who have tried all approved treatments for B-CLL another option. As most patients with B-CLL are in stage III or IV by the time both alkylating agents and fludarabine have been tried, the experience with alemtuzumab treatment are primarily with those stages of the disease. In **clinical trials**, about 30% of patients had a partial response to the drug, with 2% of these being complete responses.

This antibody has been tested with limited success in the treatment of non-Hodgkin's lymphoma (NHL) and for the preparation of patients with various immune cell malignancies for **bone marrow transplantation**. There is also a clinical trial ongoing to test the ability of this antibody to prevent rejection in kidney transplantation.

Description

Alemtuzumab is produced in the laboratory using genetically engineered single clones of B cells. Like all antibodies, it is a Y-shaped molecule can bind one particular substance, the antigen for that monoclonal antibody. For alemtuzumab, the antigen is CD52, a protein found on the surface of normal and malignant B and T cells as well as other cells of the immune and male reproductive systems. Alemtuzumab is a humanized antibody, meaning that the regions that bind CD52, located on the tips of the Y branches, are derived from rat antibodies, but the rest of the antibody is human sequence. The presence of the human sequences helps to reduce the **immune response** by the patient against the antibody itself, a problem seen when complete mouse antibodies are used for cancer therapies. The human sequences also help to ensure that the various cell-destroying mechanisms of the human immune system are properly triggered with binding of the antibody.

Alemtuzumab was approved in May of 2001 for the treatment of refractory B-CLL. It is approved for use alone but clinical trials have tested the ability of the antibody to be used in combination with the purine analogs **pentostatin**, fludarabine, and **cladribine**, and **rituximab**, a monoclonal antibody specific for the CD20 antigen, another protein found on the surface of B cells.

Recommended dosage

This antibody should be administered in a gradually escalating pattern at the start of treatment and any time administration is interrupted for 7 or more days. The recommended beginning dosage for B-CLL patients is a daily dose of 3 mg of Campath administered as a 2-hour IV infusion. Once this amount is tolerated, the dose is increased to 10 mg per day. After tolerating this dose, it can be increased to 30 mg, administered three days a

week. Acetominophen and **diphenhydramine** hydrochoride are given thirty to sixty minutes before the infusion to help reduce side effects.

Additionally, patients generally receive anti-infective medication before treatment to help minimize the serious opportunistic infections that can result from this treatment. Specifically, trimethoprim/sulfamethoxazole (to prevent bacterial infections) and famciclovir (to prevent viral infections) were used during the clinical trial to decrease infections, although they were not eliminated.

Precautions

Blood studies should be done on a weekly basis while patients are receiving the alemtuzumab treatment. Vaccination during the treatment session is not recommended, given the T cell depletion that occurs during treatment. Furthermore, given that antibodies like alumtuzumab can pass through the placenta to the developing fetus and in breast milk, use during pregnancy and breastfeeding is not recommended unless clearly needed.

Side effects

A severe side effect of alemtuzumab treatment is the possible depletion of one or more types of blood cells. Because CD52 is expressed on a patient's normal B and T cells, as well as on the surface of the abnormal B cells, the treatment eliminates both normal and cancerous cells. The treatment also seems to trigger autoimmune reactions against various other blood cells. This results in severe reduction of the many circulating blood cells including red blood cells (**anemia**), white blood cells (**neutropenia**), and clotting cells (**thrombocytopenia**). These conditions are treated with blood transfusions. The great majority of patients treated exhibit some type of blood cell depletion.

A second serious side effect of this drug is the prevalence of opportunistic infections that occurs during the treatment. Serious, and sometimes fatal bacterial, viral, fungal, and protozoan infections have been reported. Treatments to prevent **pneumonia** and herpes infections reduce, but do not eliminate these infections.

The majority of other side effects occur after or during the first infusion of the drug. Some common side effects of this drug include **fever** and chills, **nausea and vomiting**, **diarrhea**, shortness of breath, skin rash, and unusual **fatigue**. This drug can also cause low blood pressure (hypotension).

In patients with high tumor burden (a large number of circulating malignant B cells) this drug can cause a side effect called **tumor lysis syndrome**. Thought to be due to the release of the lysed cells' contents into the blood stream, it can cause a misbalance of urea, uric acid, phosphate, potassium, and calcium in the urine and blood. Patients at risk for this side effect must keep hydrated and can be given **allopurinol** before infusion.

KEY TERMS

Alkylating agent—A chemical that alters the composition of the genetic material of rapidly dividing cells, such as cancer cells, causing selective cell death; used as a chemotherapeutic agent to treat B-CLL.

Antibody—A protective protein made by the immune system in response to an antigen, also called an immunoglobulin.

Autoimmune—An immune reaction of a patient against their own cells.

Humanization—Fusing the constant and variable framework region of one or more human immunoglobulins with the binding region of an animal immunoglobulin, done to reduce human reaction against the fusion antibody.

Monoclonal—Genetically engineered antibodies specific for one antigen.

Tumor lysis syndrome—A side effect of some immunotherapies, like monoclonal antibodies, that lyse the tumor cells, due to the toxicity of flooding the bloodstream with such a quantity of cellular contents.

Interactions

There have been no formal drug interaction studies done for alemtuzumab.

See also Monoclonal antibodies; Rituximab

Michelle Johnson, M.S., J.D.

Allopurinol

Definition

This medication, also known as (Zyloprim), is used for the treatment and prevention of gout attacks and certain types of kidney stones. It is also used to treat elevated uric acid levels in the blood and urine, which can occur in patients receiving **chemotherapy** for the treat-

ment of leukemia, **lymphoma** and other types of cancer. If left untreated, high uric acid levels in patients receiving cancer chemotherapy can cause kidney stones and kidney failure.

Description

Allopurinol decreases uric acid levels in the blood and urine by inhibiting a certain enzyme responsible for production of uric acid. It has been used for over three decades for prevention of gouty arthritis, kidney stones, and **tumor lysis syndrome** in cancer patients.

Recommended Dosage

Adults

GOUT 200-300 mg per day for mild gout and 400-600 mg per day for severe gout. Patients greater than 65 years of age should be started at 100 mg per day. Their dose can be increased until desired uric acid levels in the blood are reached.

Children over 10 years of age and adults

PREVENTION OF URIC ACID KIDNEY STONES IN CANCER PATIENTS 600-800 mg per day divided into several doses, usually starting 1-2 days before cancer chemotherapy and stopped two to three days after the chemotherapy is completed for that cycle.

Total daily dose greater than 300 mg should be given in divided doses.

Children less than 10 years of age

PREVENTION OF URIC ACID KIDNEY STONES IN CANCER PATIENTS 10 mg per kg per day of allopurinol in two to three divided doses up to a maximum dose of 800 mg per day. Another alternative is to give 150 mg per day in three divided doses for children 6 years of age and 300 mg per day in two to three divided doses for children 6-10 years of age.

Administration

Allopurinol should be taken after meals to avoid stomach upset. Patients should drink plenty of fluids (at least eight glasses of water per day) while taking this medicine unless otherwise directed by a physician. Drinking a lot of water can prevent formation of kidney stones.

Precautions

The use of allopurinol in pregnant women should be avoided whenever possible because its effects on the human fetus are not known.

Allopurinol should be used with caution by the following populations:

- Patients who have had an allergic reaction to allopurinol in the past.
- Patients who are taking certain medicines for high blood pressure such as diuretics (water pills) or angiotensin converting enzyme (ACE) inhibitors (captopril, lisinopril, enalapril). These people may be at higher risk of hypersensitivity with allopurinol.
- Breast-feeding mothers.
- Children (except those who have high uric acid levels caused by cancer, chemotherapy, or genetic diseases).

Patients should call a doctor immediately if any of these symptoms develop:

- rash, **itching**, swelling of lips or mouth, trouble breathing (also known as hypersensitivity reaction)
- yellowing of the skin or eyes
- pain when urinating or blood in the urine
- unusual bleeding or bruising

Patients with kidney problems may need to use lower doses of allopurinol.

Patients taking allopurinol will need to see a physician before starting therapy and occasionally during therapy to do blood tests for monitoring of kidney and liver function and complete blood count.

Side effects

Allopurinol is usually well tolerated by most patients. The most common side effect is skin rash, hives and itching. Loss of hair, **fever**, and feelings of discomfort or uneasiness can happen alone or in combination with a rash. The risk of rash is higher in people with kidney disease or people taking amoxicillin or ampicillin. The use of allopurinol should be discontinued at first sign of a rash. Other side effects include nausea, vomiting, decreased kidney function and drowsiness (especially during the first few days of therapy). Because allopurinol can cause drowsiness, caution should be taken when performing tasks requiring alertness, such as cooking or driving.

Interactions

Patients should consult their doctor before drinking alcoholic beverages; alcohol can decrease the effectiveness of allopurinol. People consuming large amounts of vitamin C can be at an increased risk for kidney stones.

KEY TERMS

ACE inhibitors—A group of drugs used to treat high blood pressure. These drugs work by decreasing production of a certain chemical in the kidneys that causes constriction of blood vessels.

Gout—A disease, especially common in men, in which patients may have high uric acid levels in the blood and sudden attacks of severe joint pain and swelling caused by the deposits of uric acid crystals in those joints. These gout attacks most commonly affect the big toe.

Kidney stone—A concretion in the kidney made of various materials, such as uric acid crystals, calcium, or lipids. These concretions, or stones, cause severe pain when they are transported from the kidney into the bladder and out of the body.

Tumor lysis syndrome—A potentially life-threatening condition caused by cancer chemotherapy associated with very high blood levels uric acid, phosphate, and potassium, low calcium, and acute kidney failure.

Uric acid—White, poorly soluble crystals found in the urine. Sometimes uric acid forms small solid stones or crystals that are deposited in different organs in the body, such as the kidney. High levels of uric acid can be seen in patients with gout or cancer.

Allopurinol can prolong the effects of blood thinners such as **warfarin** (Coumadin) and put patients at risk for bleeding. It can also increase chances of low blood sugar with chlorpropamide (Diabinese) and nerve toxicity with vidarabine. Allopurinol can decrease breakdown of **azathioprine** (Imuran), **mercaptopurine** (6-MP), **cyclosporine** (Neoral, Sandimmune) and theophylline (Theo-Dur, Theolair, Theo-24) by the liver, increasing blood levels and side effects. Doses of azathioprine and mercaptopurine need to be reduced when they are used together with allopurinol. Mercaptopurine can be substituted for **thioguanine** (6-TG) to avoid this interaction altogether.

The use of amoxicillin and ampicillin should be avoided if possible in patients taking allopurinol because of increased risk of rash. Water pills such as hydrochlorthiazide (Diuril) can increase the risk of toxicity and allergic reaction when used with allopurinol.

Olga Bessmertny, Pharm.D.

Alopecia

Description

Alopecia, also called hair loss, baldness, and epilation, is a common side effect of **chemotherapy** and **radiation therapy**. Most patients undergoing chemotherapy, especially those who are being treated with more than one drug, will suffer from hair loss. Radiation therapy causes hair loss only in the area of skin being treated.

Although most often associated with head hair, alopecia can occur on any part of the body. Cancer treatments can also cause hair on the face (including the eyelashes and eyebrows), genitals, underarms, and body to fall out.

Alopecia usually occurs between two and three weeks after the first treatment. Most often, hair loss is gradual and occurs over a three-to-four week period. However, the chemotherapy drug **paclitaxel** can cause all the hair of the body to fall out within a 24-hour period. Loss of head hair usually begins on the top (crown) and sides of the head, presumably due to friction caused by pillows, bed linens, and hats.

Alopecia caused by chemotherapy is usually temporary. Hair loss caused by radiation therapy may be permanent. Hair typically regrows in about three to five months. Regrown hair may be a different color or type than before treatment.

Although alopecia is a harmless, painless condition, it can significantly affect **body image**, self esteem, and **sexuality**. As a result, alopecia may cause the patient to limit social activities. Hair loss can also cause **depression**.

Causes

To understand the cause of alopecia, it is helpful to understand how hair grows. Hair grows out of microscopic depressions in the skin called hair follicles. Normally, there are about 100,000 hairs on a person's head (scalp). Each hair is in one of three different growth stages. Eighty-eight percent of the hair on the head is in the growing (anagen) stage, which lasts for two to five

years. Some of the hairs are no longer growing and are in a resting (telogen) stage. The telogen stage lasts for three to five months. The transitional (catagen) stage lies between the growing and resting stages. At the end of the telogen stage, the hair falls out. Usually about 100 hairs fall out each day. Alopecia becomes noticeable only after about half of the hairs have fallen out.

Chemotherapy-induced alopecia

Chemotherapy drugs kill the rapidly growing cancer cells. However, certain normal cells of the body are rapidly growing and they, too, are affected by the chemotherapy drugs. Rapidly growing cells are found in the base of the hair (hair bulb), as well as other parts of the body. When the drug kills the cells of the hair bulb, the hair falls out. Alternatively, the drug affects the hair bulb, causing the hair to narrow. This weakened hair is prone to breakage during normal brushing or shampooing.

Although many chemotherapy drugs can cause alopecia, certain ones are highly prone to causing hair loss. In addition, the way in which the drug is administered, the dose, and the treatment schedule can influence a drug's ability to cause alopecia. For instance, the fast administration of large doses of drug (bolus-dosing) is more toxic to the hair bulb than administering lower doses more slowly. Chemotherapy drugs with a very high potential to cause alopecia include:

- **cyclophosphamide**
- **daunorubicin**
- **doxorubicin** (at doses higher than 50 mg)
- **etoposide**
- **ifosamide**
- **paclitaxel**
- **docetaxel** (taxotere)

Radiation-induced alopecia

Like chemotherapy, radiation kills rapidly dividing cells. Hair loss occurs only at the site where radiation is applied. A high dose of radiation (greater than 6,000 cGy) usually causes permanent damage to hair follicles preventing hair from regrowing. If hair regrowth occurs, the hairs may be finer than before radiation therapy. However, hair usually regrows following low doses of radiation (less than 6,000 cGy).

Treatments

Methods to prevent chemotherapy-induced alopecia exist, although their safety and effectiveness remain questionable. One method puts pressure on the scalp (scalp tourniquet) to block blood flow, thereby preventing the drugs from damaging the hair follicles. Another method uses ice or cooling devices (scalp hypothermia) to decrease the amount of drug taken up by the hair cells. Lastly, certain medications have been used to prevent alopecia.

Alopecia resulting from cancer treatment is unavoidable and no treatments for it are available. However, scientists are always working on new treatments for alopecia. In 2004, a company announced preclinical trials showed results with no harmful effects to the skin for a topical formula to treat male baldness and hair loss from chemotherapy. The medication will have to be tested on human patients and receive approval before it becomes available, which could take years. Until then, patients are encouraged to buy a wig before their hair falls out so that a good color and texture match can be made and the wig will be available when needed. Patients with long hair can have a wig made with their own hair. If a wig is covered by insurance, a doctor's prescription will be required to make an insurance claim. Some patients prefer to shave their head once hair loss begins.

Steps that a cancer patient can take to treat an irritated and red scalp and minimize hair loss include:

- using a mild shampoo
- using hair brushes with soft bristles
- avoiding the use of hair dryers, hot curlers, and curling irons
- using the lowest setting on a hair dryer (if a dryer must be used)
- avoiding hair dyes
- avoiding permanent wave solutions
- wearing sunscreen or a hat when outdoors
- using a satin pillowcase

Alternative and complementary therapies

Patients suffering from alopecia may benefit from taking certain **vitamins** and minerals that promote healthy hair. These include zinc, selenium, magnesium, iron; and vitamins A, B-complex, C, and E. Vitamin E may be massaged into the scalp. Also, evening primrose oil and flaxseed oil are rich sources of omega-3 and omega-6 fatty acids, which are important for healthy hair.

Chinese medicinal herbs that promote hair growth include cornus, Chinese foxglove root, Chinese yam, lycium fruit, and polygonum. Herbalists recommend

KEY TERMS

Anagen stage—The growing stage in the growth cycle of hair.

Catagen stage—The intermediate stage in the hair-growth cycle during which proliferation ceases and regression of the hair follicle occurs.

Hair bulb—The base of a hair where living cells multiply causing the hair to grow.

Hair follicle—The depression in skin where a hair originates.

Scalp tourniquet—A process to prevent chemotherapy-induced alopecia in which a tight band is applied to the head.

Telogen stage—The resting stage in the growth cycle of hair.

rinsing hair with sage tea or massaging the scalp with essential oil of rosemary to improve blood circulation and stimulate hair follicles.

It is important that patients check with their oncologist prior to taking any vitamin, mineral, or medicinal herb supplements as there is a possibility they may interfere with the effectiveness of the chemotherapy treatments.

Resources

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Belinda Rowland, Ph.D.
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Alternative therapies *see* **Complementary cancer therapies**

Altretamine

Definition

Altretamine, also known by the brand name Hexalen, is an anticancer agent used to treat **ovarian cancer**.

Purpose

Altretamine is used to treat persistent or recurrent ovarian cancer, usually after treatment of the cancer with **cisplatin** and/or an alkylating agent fails to effectively treat the tumor.

Description

The mechanism of action of altretamine is not known. However, it is thought that it may inhibit DNA and RNA synthesis.

Recommended dosage

Alretamine is administered orally. Doses for the drug may be different depending on the protocol that is used by the physician. Some example dosing regimens are: 4 to 12 mg per kg in three to four divided doses for 21 to 90 days; 240 to 320 mg per square meter of body surface area in three to four divided doses for 21 days, repeated every six weeks; 260 mg per square meter of body surface area per day for 14 to 21 days of a 28 days cycle in four divided doses; or 150 mg per square meter of body surface area in three to four divided doses for 14 days of a 28 day cycle. The dose of altretamine may be decreased if the patient has intolerable stomach side effects, low blood count of cells that fight infection (white blood cells) or cells that prevent bleeding (platelets), or if the patient has progressive toxicity affecting the nerves of the brain and body.

KEY TERMS

Antiemetic—Agents used to alleviate nausea and vomiting, used during and sometimes following treatment with chemotherapy or radiotherapy.

Peripheral neuropathy—Symptoms resulting from damage to the peripheral nerves, that is, nerves not found in the spinal cord or brain.

Precautions

Caution is usually taken in prescribing altretamine to patients with decreased kidney or liver function or damage to nerves due to previous **chemotherapy**. Careful monitoring of nerve, kidney, and liver function is required for these patients.

Pregnant women should be warned before taking this drug, as it may cause permanent harm to the fetus. Women who are of childbearing age should apply contraceptive methods to avoid pregnancy until they have discontinued drug use. Altretamine may also affect fertility. Additionally, although it is not known whether this drug is excreted in the breast milk, nursing mothers are cautioned not to breast feed while being treated with altretamine.

Side effects

Nausea and vomiting may gradually occur as patients receive continuous high dose of altretamine. In most instances, **antiemetics** can help control these side effects. However, some patients may experience severe nausea and vomiting that requires either reducing the dose or stopping treatment with altretamine. Other common side effects include loss of appetite (**anorexia**) and **diarrhea**. Patients may also experience nerve toxicity, which is described as numbness, tingling, and burning sensations in the fingers and toes. Patients can also have difficulty walking because of these sensation changes. Patients may also commonly experience: **thrombocytopenia**, a decrease of the platelet cells responsible for blood clotting; **anemia**, a decrease of the red blood cells responsible for oxygen transport to tissues and organs; and leukopenia, a decrease of the white blood cells responsible for fighting infections. Less common side effects include seizures, **depression**, dizziness, stomach cramps, liver toxicity, rash, and hair loss (**alopecia**).

Interactions

Persons taking altretamine and monoamine oxidase inhibitors (MAO inhibitors) may experience severe hypotension (low blood pressure) when standing up. Additionally, the drug cimetidine may increase the toxicity of altretamine. Prior to starting any over-the-counter medications, herbal medications, or new medications, patients should consult with their physician, nurse, or pharmacist to ensure that there are no potential drug interactions.

Michael Zuck, Ph.D.

Amenorrhea

Definition

Amenorrhea is the absence of menstruation and is a symptom, not a diagnosis.

Primary amenorrhea refers to the absence of the onset of menstruation by age 16 whether or not normal growth and secondary sexual characteristics are present, or the absence of menses after age 14 when normal growth and signs of secondary sexual characteristics are present. Secondary amenorrhea is the absence of menses for three cycles or six months in women who have previously menstruated.

In terms of the relationship of amenorrhea to cancer, amenorrhea may be a symptom of a gynecologic tumor, or the pause or cessation in menstruation may develop as a side effect of cancer treatment.

Demographics

The prevalence of primary amenorrhea is 0.3% and secondary amenorrhea occurs in approximately 1%–3% of women. However, among college students and athletes the incidence can range from 3%–5% and 5%–60%, respectively.

For cancer-related amenorrhea, one clinician noted that nine out of ten women under his care reported secondary amenorrhea following bone marrow transplants. **Chemotherapy** and abdominal-pelvic **radiation therapy** likewise produce similar outcomes.

Causes

Normal menstrual bleeding occurs between menarche and menopause and has an average length of 28 days but varies from woman to woman. The normal menstrual cycle depends on cyclic changes in estrogen and progesterone levels, as well as the integrity of the

clotting system and the ability of the spiral arterioles in the uterus to constrict. Abnormalities in any of these components may cause bleeding to stop or increase.

Primary amenorrhea

There are multiple causes for primary amenorrhea once pregnancy, lactation and missed abortion are ruled out. These include:

- anorexia nervosa/bulimia/malnutrition
- extreme obesity
- hyperthyroidism/hypoglycemia
- congenital heart disease
- cystic fibrosis/Crohn's disease
- genetic abnormalities
- obstructions: imperforate hymen/vaginal or cervical absence
- ovarian, pituitary (**craniopharyngioma**) or adrenal tumors
- polycystic ovarian disease
- testicular feminization

It is rare for primary amenorrhea to be caused by tumors but it can be a cause and should always be a consideration if other factors are ruled out.

Gonadal failure (a nonfunctioning sex gland) is the most common cause of primary amenorrhea, accounting for almost half the patients with this syndrome. The second most common cause is uterovaginal agenesis (absence of a uterus and/or vagina) with an incidence of about 15% of individuals with this syndrome. One of the most important, and probably most common, causes of amenorrhea in adolescent girls is anorexia nervosa, which occurs in about 1 in 1,000 white women. It is uncommon in women older than 25 and rare in women of both African and Asian descent. When women lose weight 15% below ideal body weight, amenorrhea can occur due to central nervous system-hypothalamic dysfunction. When **weight loss** drops below 25% ideal body weight, pituitary gonadotrophin function (follicle stimulating hormone and luteinizing hormone) can also become abnormal.

Each year of athletic training before menarche (the beginning of menstrual function) delays menarche about four to five months. Amenorrhea associated with strenuous exercise is related to stress, not weight loss, and is most probably caused by an increase in central nervous system endorphins and other compounds which interfere with gonadotrophin-releasing hormone release.

Secondary amenorrhea

Once pregnancy, lactation and menopause are ruled out, the causes for secondary amenorrhea include:

- extreme obesity
- prolonged or extreme exercise
- anxiety or emotional distress
- non-oral contraceptives (Norplant/Depo-Provera)
- D & C (**dilatation and curettage**)(Asherman's syndrome)
- early menopause
- autoimmune dysfunction
- pituitary tumors and central nervous system lesions

Cancer and secondary amenorrhea

As mentioned, not only does amenorrhea occur as a symptom of a tumor and/or lesion, but it often develops in women undergoing treatment for cancer.

RADIATION Radiation therapy is used in conjunction with chemotherapy in a number of clinical situations, including **Hodgkin's disease** and childhood leukemia and lymphomas. Ovarian damage occurs under these circumstances to varying degrees, depending upon the total dosage of radiation as well as the age of the patient at the time of exposure.

CHEMOTHERAPY Premenopausal women receiving single or multi-agent chemotherapy are at risk for short-term amenorrhea, as well as ovarian damage. Even young women who resume menstruation following chemotherapy are at risk for early menopause; therefore, those treated in childhood and adolescence should be counseled regarding the chance of early menopause in order to plan ahead for childbearing.

WEIGHT LOSS Side effects of cancer as well as treatments can cause a decrease in appetite and **nausea and vomiting**, which, in turn, can cause severe weight loss as associated with malnutrition. Thus, menstruation may cease for the same reasons as it does in young adolescents with anorexia nervosa—hypothalamic dysfunction.

STRESS Stress has always been noted to play a large role in the cause of amenorrhea, so the actual stress of having cancer and undergoing treatments may also cause amenorrhea to occur.

RETURN OF NORMAL OVARIAN FUNCTION FOLLOWING TREATMENT Research on the recovery of normal ovarian function with young girls and/or young women has not revealed any reliable data. There are individual success stories especially with new advances in

KEY TERMS

Alkylating agents—A group of synthetic compounds that act on the deoxyribonucleic acid (DNA) in the nucleus of the cell and are used in cancer chemotherapy.

Aplastic anemia—Any form of anemia caused by defective development of bone marrow.

Asherman's syndrome—The presence of adhesions within the uterus following a D & C.

Autoimmune dysfunction—A disease associated with the production of antibodies directed against one's own tissues.

Craniopharyngioma—Tumor arising from the cells in the pituitary.

Crohn's disease—Inflammation of the gastrointestinal tract.

Imperforate hymen—The lack of an opening in the membranous fold partly or completely closing the opening to the vagina.

Intermenstrual—Time period between one menstrual cycle to another.

Luteinizing hormone—A hormone which acts with follicle-stimulating hormone to cause ovulation of mature follicles and secretion of estrogen from the ovary.

Menopause—The stage of life during which a woman passes from the reproductive to the nonreproductive stage and she experiences the cessation of menstruation.

Menses/Menstruation—The periodic discharge from the vagina of blood and tissues from a nonpregnant uterus.

Polycystic ovary disease—Also called Stein-Leventhal syndrome, it is the presence of many cysts in the ovaries.

Postcoital—Following intercourse.

Progestins—A steroid sex hormone that maintains the lining of the uterus.

Testicular feminization—An individual with female external development, including secondary sex characteristics, but with the presence of testes and absence of uterus and tubes.

assisted reproductive technologies (ARTs), but overall, the return of normal ovarian function seems to be age-dependent. One researcher recently reported on ovarian function in 65 women who underwent high-dose chemotherapy and bone marrow transplants for aplastic anemia. All women younger than 26 years at the time of chemotherapy recovered ovarian function, while 7 of the 18 women aged 26 to 38 years did not recover ovarian function. Thus, the risk of ovarian dysfunction appears to increase with advancing age when ovarian reserve decreases. Additionally, the risk of dysfunction increases with the dose of alkylating agents, notably **cyclophosphamide**.

Treatments

Even with the possibility of ovarian compromise, women previously treated for cancer have successfully achieved pregnancy via ART's. Advances in the area of ART's include the use of donor eggs, the possibility of freezing embryos, and eventual oocyte (immature ovum) pretreatment offer more options to young women facing cancer chemotherapy.

Special concerns

The need for effective contraception during and after cancer treatment is imperative. Normal menstrual cycles do not imply normal fertility and likewise, irregular menses or even amenorrhea does not imply a lack of fertility. Women with dysfunctional bleeding or amenorrhea are still capable of spontaneous ovulation and conception.

The most reliable form of birth control for any population of women is injectable progestins, which suppress luteinizing hormone secretion. Depo-Provera, 150 mg injected intramuscularly, will effectively block ovulation for four months. Norplant (six rubber capsules placed under anesthesia in the upper arm) will effectively block ovulation for five years. If the treatment or the specific cancer diagnosis contraindicates the use of either of these contraceptives, other options should be considered, i.e., sterilization for the woman or her partner, an intrauterine device (IUD), or barrier methods (condoms, diaphragm or spermicides).

See also Fertility and cancer.

Resources

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Linda K. Bennington, C.N.S., M.S.N.

American Joint Commission on Cancer

Definition

The American Joint Commission on Cancer (AJCC) is an organization dedicated to creating and promoting a universal system of classifying tumors according to their location in the body and involvement with surrounding tissues.

Description

Created in 1959, the AJCC works with the International Union Against Cancer (UICC), its European counterpart, and other organizations to standardize cancer-related information and data collection. The AJCC bases its classification on the TNM staging system, a universally accepted method of describing the extent of cancer, and other clinical information. The result is a standardized method of categorizing tumors that helps physicians to predict patient prognosis and develop treatment guidelines. The AJCC periodically publishes its *Cancer Staging Manual*, which is used widely by health care professionals in the diagnosis and treatment of cancer patients.

Tamara Brown, R.N.

See also Tumor staging.

Amifostine

Definition

Amifostine, also known as the brand name Ethyol and as ethiofos or WR2721, is a medicine that helps protect certain tissues of the body from damage caused by **chemotherapy** or **radiation therapy**.

Purpose

Amifostine is a protectant agent that is used in combination with the chemotherapy drug **cisplatin** or in combination with radiation therapy. Amifostine is approved by the Food and Drug Administration (FDA) to prevent kidney damage caused by repeat doses of the chemotherapy agent cisplatin in patients who have a diagnosis of **ovarian cancer** or non-small cell lung cancer. It is also FDA approved for patients with head and neck cancer who are receiving radiation therapy after surgery. In this group of patients, amifostine helps decrease radiation damage to the salivary glands, which can cause dry mouth.

Description

Amifostine has been on the market since the mid-1990s. A clear colorless solution, it is administered into a vein before chemotherapy and has been shown to decrease kidney damage by greater than 50% in advanced ovarian cancer patients who have received multiple cycles of cisplatin. It is also used before radiation therapy to prevent damage to the salivary gland known as the parotid gland.

When cisplatin is given to patients, it becomes broken down into toxic substances that destroy cancer cells and normal cells. When amifostine is administered into the body, it is broken down by an enzyme that occurs in large quantities in normal cells but not in cancerous cells. It then is converted into a substance called free thiol, which combines with the poisonous cisplatin by-products in the normal cells and makes them nontoxic.

In patients who receive radiation to the mouth area, including the salivary glands, the radiation causes the release of substances called free oxygen species, which damage cells of the mouth. An enzyme in cells of the mouth breaks down amifostine into a substance called free thiol. The free thiol blocks the free oxygen substances from damaging the salivary cells and decreases the amount of dry mouth patients suffer from when they receive radiation to the head and neck area.

Recommended dosage

Before dosing amifostine in chemotherapy or radiation therapy patients, intravenous fluids need to be given to keep the body well flushed with fluid and to maintain a normal blood pressure. All patients will receive amifostine lying down, sometimes with the head of the body lower than the feet. Patients should also receive medication to help prevent the **nausea and vomiting** that occurs due to amifostine.

Amifostine dosages can be determined using a mathematical calculation that measures a person's body surface area (BSA). This number is dependent upon a patient's height and weight. The larger the person, the greater the body surface area. Body surface area is measured in units known as square meter (m^2). To determine the actual dose a patient is to receive, the body surface area is calculated and then multiplied by the drug dosage in milligrams per squared meter (mg/m^2).

The recommended dosage of amifostine for protection of the kidney is $910mg/m^2$ administered as a 15-minute infusion into a vein. This is to begin 30 minutes

before chemotherapy administration. If a patient has difficulty with this dose, the dosage can be lowered to 740 mg/m^2.

The recommended dosage of amifostine for radiation therapy patients is 200 mg/m^2 administered once a day into a vein over a three-minute time period 15 to 30 minutes before the patient receives radiation treatment.

Precautions

Amifostine can cause a decrease in blood pressure when it is administered. During the 24 hours before receiving amifostine, patients need to drink a lot of liquids. When amifostine is being administered, medical personnel will be monitoring the patient's blood pressure. If the blood pressure drops significantly, the infusion of amifostine will be stopped until blood pressure returns to normal. The doctor will decide if the patient should receive any additional amifostine. Patients who have low blood pressure to begin with or patients who are not drinking a lot of fluids—referred to as being dehydrated—should not receive amifostine.

Patients with a known previous allergic reaction to aminothiol drugs should not receive amifostine.

Patients who may be pregnant, thinking of becoming pregnant, or who have a history of heart problems or strokes should tell their doctor before receiving amifostine.

Side effects

The most common side effect from receiving amifostine is a lowering of blood pressure, which occurs in approximately 62% of patients treated at a dose of 910mg/m^2. This lowering of blood pressure occurs within the first 15 minutes of administering the drug. Blood pressure is monitored throughout the infusion of amifostine. If the blood pressure drops to certain level then the drug is stopped and restarted only when blood pressure returns to normal.

Nausea and vomiting are common side effects. They occur rapidly and can be severe. Usually, patients are given medicines before receiving amifostine that can help prevent or decrease these side effects. Other side effects include sneezing, hiccups, a warm feeling and redness of the face, sleepiness and dizziness, metallic taste, **fever**, rash, and chills.

Rare side effects of amifostine are: a lowering of calcium levels in the blood, seizures, allergic reactions which include symptoms of fever, shaking chills, **itching**, low blood pressure, shortness of breath, and rashes. There have been rare reports of throat swelling, chest tightness, and heart stopping.

KEY TERMS

Chemotherapy—Specific drugs used to treat cancer.

Enzyme—A protein in the body that breaks down substances, such as food or medicines, into simpler substances that the body can use.

Food and Drug Administration—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives approval to pharmaceutical companies for commercial marketing of their products.

Intravenous—To enter the body through a vein.

Radiation therapy—The use of high-energy beams focused to treat cancerous tumors.

All side effects a patient experiences should be reported to their doctor.

Interactions

Amifostine causes a decrease in blood pressure and should be used with caution in patients who take blood pressure lowering medicines or other medications that may lower blood pressure. If patients are taking blood pressure medications, they may be asked to stop taking these medications for 24 hours before receiving amifostine.

Patients should tell their doctors if they have a known allergic reaction to amifostine or any other medications or substances, such as foods and preservatives. Before taking any new medications, including nonprescription medications, **vitamins**, and herbal medications, patients should notify their doctors.

Nancy J. Beaulieu, RPh., BCOP

Aminoglutethimide

Definition

Aminoglutethimide, also known by the brand name Cytadren, is a cancer drug which inhibits the formation of hormones like adrenal glucocorticoids, mineralocorticoids, estrogen, androgens, and aldosterone.

Purpose

Aminoglutethimide is used to treat Cushing's disease, **breast cancer**, or **prostate cancer**. It blocks the conversion of cholesterol to delta-5-pregnenolone, a precursor for the formation of the **corticosteroids**.

Description

Aminoglutethimide is used clinically to reduce the amount of the hormones that can sometimes cause tumors to grow more quickly or are necessary for the survival of the tumor. For example, estrogen is important for the growth of some breast tumors. Lowering estrogen production by the administration of aminoglutethimide might reduce tumor growth or contribute to the destruction of the tumor.

Recommended dosage

Aminoglutethimide is given orally and dosages vary from patient to patient based on a number of factors, including the underlying disease process.

Precautions

Because some corticosteroid is necessary for normal function, patients should receive steroid replacement in addition to aminoglutethimide. Patients may require more corticosteroid when undergoing surgery, illness, or other conditions that cause stress. Hormones that affect the balance of sodium in the body may also be affected by aminoglutethimide and might have to be replaced as a result. If they are not replaced, patients may experience constant low blood pressure or low blood pressure upon standing.

Pregnant women should be warned that aminoglutethimide administration could cause fetal abnormalities. Pregnant patients should consult their physician about the current state of knowledge regarding risks and alternatives before beginning administration of aminoglutethimide. Female patients of childbearing age should attempt to avoid pregnancy while taking this drug. Mothers who are nursing should discontinue nursing while taking this drug.

Side effects

Common side effects from the administration of aminoglutethimide is rash (possibly associated with **fever**) which usually occurs in the first two weeks of therapy. It is usually self-limiting and gets better in a about a week. If the rash continues after one week patient should contact his/her physician or nurse. **Fatigue** is another common side effect of the drug and usually occurs in the first week of therapy. It may take about a month before it gets better. It can be very severe in some patients and if this is the case the patient's physician or nurse should be notified. Female patients may experience masculinization: new and excessive hair growth, a deeper voice, and irregular, abnormal, or absent menstrual periods. Thyroid function may be decreased after several weeks of therapy and the patient's thyroid should be monitored by the physician. Mild **nausea and vomiting** may also occur, as well as dizziness, **depression**, shaking, difficulty speaking, and increased heart rate. Any of these effects, or other unusual symptoms, should be reported to the patient's physician.

KEY TERMS

Hormone—A substance, such as cortisol or estrogen, that causes specific effects on target organs in the body. Hormones may be required for tumor growth or survival. Hormones usually travel in the bloodstream from the organ where they originate to a different organ where they have their effect.

Interactions

Dexamethasone, blood-thinning medications, theophylline, and digoxin doses for patients taking aminoglutethimide may need to be increased by the physician. Patients should tell their doctors if they have a known allergic reaction to aminoglutethimide medications or substances, such as foods and preservatives. Before taking any new medications, including nonprescription medications, **vitamins**, and herbal medications, patients should notify their doctors.

Michael Zuck, Ph.D.

Amitriptyline

Definition

Amitriptyline is a medication used to treat various forms of **depression**, pain associated with the nerves (neuropathic pain), and to prevent migraine headaches. It is sold in the United States under the brand name Elavil.

Purpose

Amitriptyline helps relieve depression and pain. It is often used to manage nerve pain resulting from cancer

treatment. Such injury to nerves causes a burning, tingling sensation. This medication, usually given at bedtime, helps patients sleep better.

Description

This medication is one of several tricyclic antidepressants. Amitriptyline acts to block reabsorption of chemicals that transmit nerve messages in the brain.

Recommended dosage

Amitriptyline's usual adult dose for pain management is 10 mg to 150 mg at bedtime. Patients are generally started on a low dose. The amount of medication may be increased as needed. Side effects, such as a dry mouth and drowsiness, may make it difficult to increase the dose in older adults. Bedtime dosing helps the patient sleep. Doctors generally order 75 mg to 150 mg for depression. It is given at bedtime or in divided doses. It may take 30 days for the patient to feel less depressed. Pain relief is usually noticed sooner than the mood change. Teens and older adults usually receive a lower dose. If the nightly dose is missed, it should not be taken the next morning. Taking amitriptyline during waking hours could result in noticeable side effects. Patients should check with their doctor if the daily dose is missed. Those on more than one dose per day should take a missed dose as soon as it is noted. Patients should not take two doses at the same time. Injectable amitriptyline is available. It should not be used long-term. Patients should switch to tablets as soon as possible.

Precautions

Patients should not suddenly stop taking this medication. The dose should gradually be decreased, then discontinued. If the drug is abruptly stopped, the patient may experience headache, nausea, discomfort throughout the body, and a worsening of original symptoms. Amitriptyline's effects last for three to seven days after the medication has been stopped. Older adults usually are more prone to some side effects. These include drowsiness, dizziness, mental confusion, blurry vision, dry mouth, difficulty urinating, and constipation. Taking a lower dose may help resolve these problems. Patients may need to stop this medication before surgery.

Amitriptyline should not be given to anyone with allergies to the drug or to patients recovering from a heart attack. Patients taking MAO inhibitors, a different type of antidepressant, should not also use amitriptyline. It should be administered with caution to patients with glaucoma, seizures, urinary retention, an overactive thyroid, poor liver or kidney function, alcoholism, asthma, digestive disorders, an enlarged prostate, seizures, or heart disease. This medication should not be given to children under 12. Pregnant women should discuss the risks and benefits of this medication with their doctor. Fetal deformities have been associated with taking this drug during pregnancy. Women should not breastfeed while using amitriptyline.

KEY TERMS

MAO inhibitor—A type of antidepressant medication

Side effects

Common side effects associated with amitriptyline include dry mouth, drowsiness, constipation, and dizziness or lightheadedness when standing. Patients can suck on ice cubes or sugarless hard candy to combat the dry mouth. Increased fiber in the diet and additional fluids may help the constipation. The dizziness is usually caused by a drop in blood pressure when changing position. Patients should slowly rise from a sitting or lying position if dizziness is noticed. Amitriptyline may increase the risk of falls in older adults. Patients should not drive or operate machinery or appliances while under the influence of this drug. Alcohol and other central nervous system depressants can increase drowsiness. Amitriptyline may also produce blurry vision and an irregular or fast heartbeat. Amitriptyline also may raise or lower blood pressure, or cause palpitations. This medication may increase or decrease diabetic patients' blood sugar levels. Amitriptyline may make patients' skin more sensitive to the sun. Patients should avoid direct sunlight, wear protective clothing, and apply sunscreen with a protective factor of 15 or higher.

Amitriptyline may increase appetite, cause weight gain, or produce an unpleasant taste in the mouth. It may also cause **diarrhea**, vomiting, or heartburn. Taking this medication with food may decrease digestive side effects. Other less likely side effects include muscle tremors, nervousness, impaired sexual function, sweating, rash, **itching**, hair loss, ringing in the ears, or changes in the make up of the patient's blood. Patients with schizophrenia may develop an increase in psychiatric symptoms.

Interactions

Patients should always tell all doctors and dentists that they are taking this medication. Amitriptyline may decrease the effectiveness of some drugs used to treat high blood pressure. Amitriptyline should not be taken with other antidepressants, epinephrine and other adrena-

line-type drugs, or methylphenidate. Patients should not take over-the-counter medications without checking with their doctor. For instance, amitriptyline should not be taken with Tagamet (cimetidine) or Neo-Synephrine. Patients taking this drug should avoid the dietary supplements St. John's wort, belladonna, henbane and scopolia. Black tea may decrease the absorption of this drug. Patients should ingest the drug and tea at least two hours apart.

Debra Wood, R.N.

Amphotericin B *see* **Antifungal therapy**

Amphotericin B liposomal *see* **Antifungal therapy**

Amputation

Definition

Amputation is the intentional surgical removal of a limb or body part. It is performed to remove diseased tissue or relieve pain.

Purpose

Arms, legs, hands, feet, fingers, and toes can all be amputated. Most amputations involve small body parts such as a finger, rather than an entire limb. More than 60,000 amputations are performed in the United States each year.

Amputation is performed for the following reasons:

- to remove tissue that no longer has an adequate blood supply
- to remove malignant cancers (almost exclusively in the case of osteogenic sarcoma or other sarcomas)
- as a result of severe trauma to the body part

The blood supply to an extremity can be cut off because of injury to the blood vessel, hardening of the arteries, arterial embolism, impaired circulation as a complication of diabetes mellitus, repeated severe infection that leads to gangrene, severe frostbite, Raynaud's disease, or Buerger's disease.

More than 90% of amputations performed in the United States are due to circulatory complications of diabetes, the most common cause of non-traumatic leg and foot amputations.

Precautions

Amputation cannot be performed on patients with uncontrolled diabetes mellitus, heart failure, or infection, and is also inadvisable for patients with blood clotting disorders.

Description

Amputations can be either planned or emergency procedures. Injury and arterial embolisms are the main reasons for emergency amputations. The operation is performed under regional or general anesthesia by a general or orthopedic surgeon in a hospital operating room.

Details of the operation vary slightly depending on what is to be removed. The goal of all amputations is twofold: to remove diseased tissue so that the wound will heal cleanly, and to construct a stump that will allow the attachment of a prosthesis or artificial replacement part.

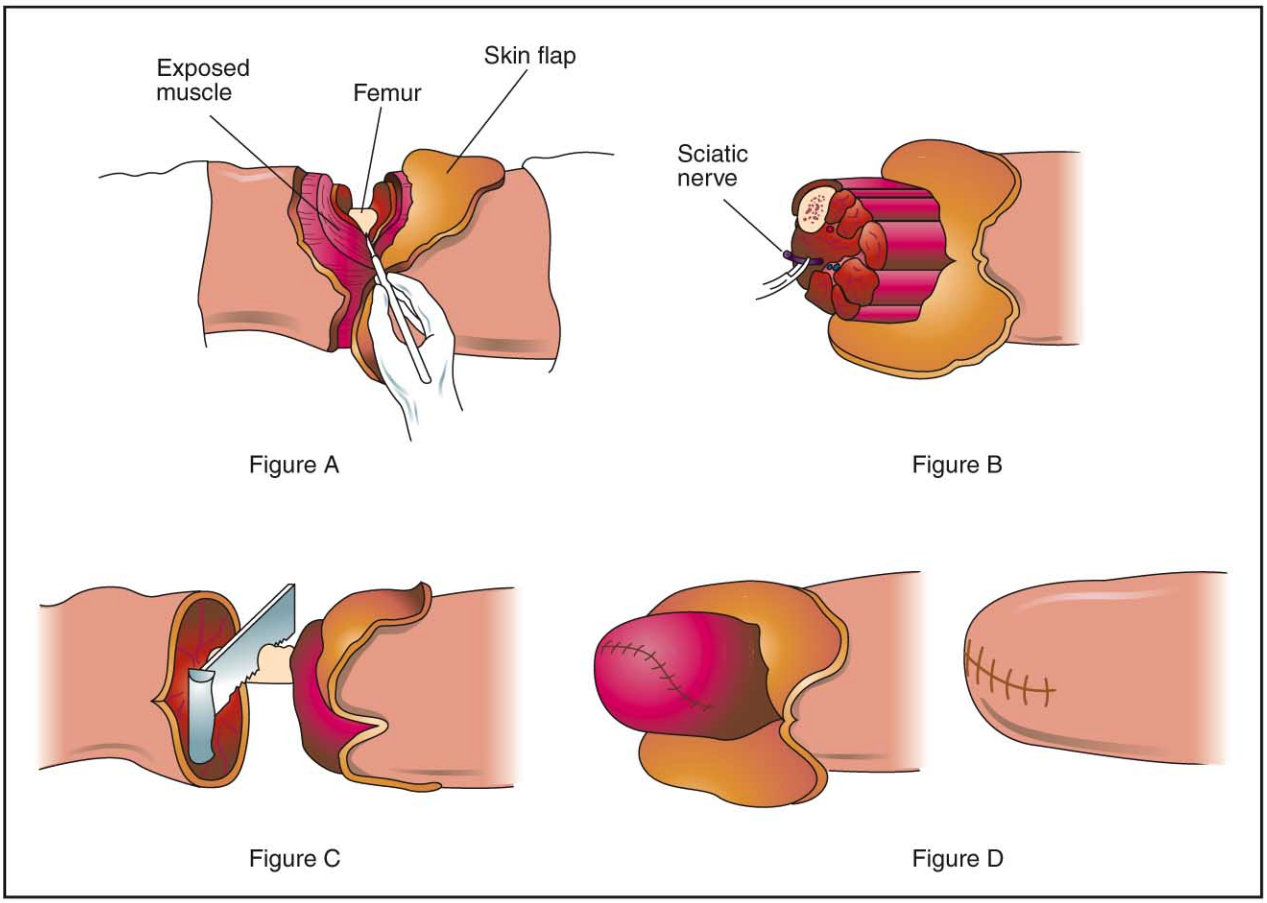
The surgeon makes an incision around the part to be amputated. The part is removed, and the bone is smoothed. A flap is constructed of muscle, connective tissue, and skin to cover the raw end of the bone. The flap is then closed over the bone with sutures (surgical stitches) that remain in place for 3 to 4 weeks. Often, a rigid dressing or cast is applied that stays in place for about two weeks.

Preparation

Before an amputation is performed, extensive testing is done to determine the proper level of amputation. The goal of the surgeon is to find the place where healing is most likely to be complete, while allowing the maximum amount of limb to remain for effective rehabilitation.

The greater the blood flow through an area, the more likely healing is to occur. These tests are designed to measure blood flow through the limb. Several or all of the following can be done to help choose the proper level of amputation:

- measurement of blood pressure in different parts of the limb
- Xenon 133 studies, which use a radiopharmaceutical to measure blood flow
- Oxygen tension measurements in which an oxygen electrode is used to measure oxygen pressure under the skin. If the pressure is 0, healing will not occur. If the pressure reads higher than 40ml Hg (40 milliliters of mercury), healing of the area is likely to be satisfactory.
- laser Doppler measurements of the microcirculation of the skin



Amputation of leg. A: The muscle is cut and the main artery exposed. B: The surgeon severes the main artery and veins. C. The surgeon saws through the femur bone. D. The muscles are sutured over the bone *(Illustration by Electronic Illustrators Group. Reproduced by permission of The Gale Group.)*

- skin fluorescent studies that also measure skin microcirculation
- skin perfusion measurements using a blood pressure cuff and photoelectric detector
- infrared measurements of skin temperature

No one test is highly predictive of healing, but taken together, the results can give the surgeon a detailed idea of the best place to amputate.

Aftercare

After amputation, medication is prescribed for pain, and patients are treated with **antibiotics** to discourage infection. The stump is moved often to encourage good circulation. Physical therapy and rehabilitation are started as soon after surgery as possible. Studies have shown that there is a positive relationship between early rehabilitation and effective functioning of the stump and prosthesis. Length of stay in the hospital depends on the severity of the amputation and the general health of the amputee, but is usually less than one week.

Recovery from surgery takes about six weeks. Rehabilitation, however, is a long and arduous process, especially for above-the-knee amputees. The doctor and physical therapist decide how soon after surgery the patient can begin to exercise, and several sessions each day may be recommended. In addition, psychological counseling is an important part of rehabilitation. Many patients experience a sense of loss and grief when they lose a body part. Others are bothered by phantom limb syndrome, where they feel as if the amputated part is still in place. They may even feel pain in the limb that has been removed. Many amputees benefit from joining self-help groups and meeting others who are also living with amputation. Addressing the emotional aspects of amputation often speeds the physical rehabilitation process.

Risks

Amputation is a major surgery. All the risks associated with the administration of anesthesia exist, along with the possibility of heavy blood loss and the development of blood clots. Infection is of special concern to

amputees. If the stump becomes infected, it is necessary to remove the prosthesis and sometimes to amputate a second time at a higher level.

Failure of the stump to heal is another major complication. Nonhealing is usually due to an inadequate blood supply. The rate of complications is generally lowest in centers that specialize in amputation.

As many as 80% of amputees experience some degree of sensation in the stump or phantom limb, and 5% to 10% seek medical attention for the pain. Although phantom pain is most common in the year following amputation, it can be a long-term problem that persists in spite of therapy. One final complication is that many amputees give up on the rehabilitation process and discard their prosthesis. Better fittingprosthetics and earlier rehabilitation have decreased the incidence of this problem. Researchers and prosthetic manufacturers continue to refine the materials and methods used to try to improve the comfort and function of prosthetic devices for amputees. For example, a 2004 study showed that a technique called the bone bridge amputation technique helped improve comfort and stability for transtibial amputees.

Normal results

The wound should heal fully within four to eight weeks and the patient will have no surgery-associated complications. Some patients may begin practicing with artificial limbs as soon as 10 to 14 days following surgery.

Abnormal results

The most common complications of amputation are:

- massive hemorrhage that occurs when a suture becomes loose
- infection
- rash, blisters, and skin breakdown caused by immobility, pressure, and other sources of irritation
- pneumonia, blood clots, and breathing problems associated with immobility
- formation of nerve cell tumors (neuromas) at severed nerve endings

Complications can develop immediately after surgery or after the patient has left the hospital. The doctor should be notified if a patient who has had an amputation experiences:

- increased pain, swelling, or drainage at the site of the surgery
- headache, muscle aches, dizziness, a general ill feeling, **fever**, or other signs of infection
- nausea
- vomiting
- chest pain
- constipation
- coughing
- shortness of breath
- changes in skin quality (certain areas become chalky or blackened)
- any new symptoms

KEY TERMS

Arterial embolism—A blood clot arising from another location that blocks an artery.

Buerger's disease—An episodic disease that causes inflammation and blockage of the veins and arteries of the limbs. It tends to be present almost exclusively on men under age of 40 who smoke, and may require amputation of the hand or foot.

Diabetes mellitus—A disease in which insufficient insulin is made by the body to metabolize sugars.

Raynaud's disease—A disease found mainly in young women that causes decreased circulation to the hands and feet. Its cause is unknown.

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ORGANIZATIONS

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Amputation Information Resource Center. 6480 Wayzata Blvd., Minneapolis, MN 55426.

Amputation Prevention Global Resource Center. <http://www.diabetesresource.com>.

Cherub Association of Families and Friends of Limb Disordered Children, Inc. 8401 Powers Rd., Batavia, NY 14020.(716) 662-9997.

National Amputation Foundation. 73 Church St., Malverne, NY 11565. (516) 887-3600. <http://www.nationalamputation.org>.
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Tish Davidson, A.M.
Teresa G. Odle

Amsacrine

Definition

Amsacrine is an antitumor agent used to treat adult **acute leukemia**. It is no longer commercially available in the United States, although it is available in Canada.

Purpose

Amsacrine is an **investigational drug** used to treat refractory acute lymphocytic and nonlymphocytic leukemias, **Hodgkin's disease**, and non-Hodgkin's lymphoma. It may also have some activity against **head and neck cancers**.

Description

Amsacrine inhibits the synthesis of DNA. It also inhibits the enzyme responsible for cutting the strands of DNA, and untwists DNA so that replication of DNA cannot occur.

Recommended dosage

The dose for amsacrine may be different depending on the protocol used by the physician. The drug is given through the vein as a 30- to 90- minute infusion or as a 24-hour continuous infusion. Example doses for adults are: 60 to 160 mg per square meter of body surface area every three to four weeks, or 40 to 120 mg per square meter of body surface area for five to seven days every three to four weeks. The dose for children is 120 to 150 mg per square meter of body surface area per day for five days. The dose of amsacrine is usually decreased in patients with decreased kidney or liver function.

Precautions

Amsacrine is usually given with caution to patients with underlying heart disease, severe kidney or liver disease, or to patients who have received high doses of anthracycline **chemotherapy** drugs, such as **doxorubicin**.

Although the effects of amsacrine treatment on children are currently unknown, caution is still indicated. Women of childbearing age should take precautions to prevent pregnancy while on this drug. Women should not breastfeed while taking this medication.

Side effects

Toxicity to the heart is a common side effect of amsacrine, and patients receiving this drug are usually very closely monitored by their physician. Other common side effects of amsacrine include **nausea and vomiting**, **diarrhea**, ulcerations of the mouth and the gastrointestinal tract, decreased white blood cells and platelets, and decreased liver function. Patients may notice orange-red discoloration of the urine, but should not be alarmed as this is normal. The urine will clear again once all the drugs have been eliminated from the body. Other common side effects include headache, dizziness, confusion, seizures, abnormal touch sensation such as burning and prickling, and blurred vision. As with any side effects that occur while taking any medications, patients should notify their doctor or nurse immediately.

Interactions

To prevent any drug interactions, patients should consult their physician, nurse, or pharmacist prior to taking any over-the-counter medications, herbal medications, or new medications. Many physicians recommend bringing the containers with the names of the drugs to an appointment.

Michael Zuck, Ph.D.

Anagrelide

Definition

Anagrelide, also known by the brand name Agrylin, is used to treat patients with thrombocytosis, a condition in which patients have too many platelet cells in their

KEY TERMS

Platelets—A cell type found in the blood important for blood clotting.

Thrombocytosis—The condition of having too many platelet cells in the blood.

blood. Platelets are a cell type formed in the bone marrow that are involved in the blood clotting process.

Purpose and description

Anagrelide reduces the platelet count in patients with blood disorders.

Recommended dosage

Adult patients taking anagrelide should receive 0.5 mg of the drug four times daily or one mg twice daily. Based on the response to therapy, the dose of anagrelide can be increased by 0.5 mg per day every seven to 14 days if necessary. The goal is to maintain platelets at a count of less than 600,000 at the lowest dose of the drug possible to keep side effects at a minimum.

Precautions

Patients with heart disease should be given anagrelide with caution. Anagrelide should be given with caution, if at all, in patients taking drugs that affect platelet aggregations such as aspirin, clopidrogel, ticlopodine, or non-steroidal agents.

Pregnant mothers should be warned that anagrelide administration may cause fetal abnormalities. Pregnant patients should consult their physician about the current state of knowledge regarding risks and alternatives before beginning administration of anagrelide. Female patients of childbearing age should attempt to avoid pregnancy while taking this drug. Mothers who are nursing should discontinue nursing while taking this drug.

Side effects

The most common side effects of anagrelide are palpitations, fluid gain resulting in swelling, headaches, dizziness, **diarrhea**, stomach discomfort, mild to moderate nausea, passing gas, weakness, shortness of breath, and decreased platelets. Less common side effects of anagrelide include increased heart rate and chest pain, malaise, rash, vomiting, and decreased appetite. As with all medications, patients should contact their physician or nurse if any of these side effects occur.

Interactions

There are no proven interactions between anagrelide and other drugs. The drug sucralfate may interfere with the absorption of anagrelide. Prior to starting any over-the-counter medications, herbal medications, or new medications, patients should consult their physician, nurse, or pharmacist to prevent drug interactions.

Michael Zuck, Ph.D.

Anal cancer

Definition

Anal cancer is an uncommon cancer occurring in the tissues that make up the opening through which stool passes out of the body.

Description

The anus is the opening at the end of the large intestine (rectum) through which solid waste passes out of the body. The anus is a junction between two types of tissues: mucosa, which lines the intestines, and skin. Cancer located at the junction between the rectum and anus is called "anal canal cancer" (also known as transitional cell, squamous, epidermoid, or basal cell cancer). Cancer located near the external skin is called "anal margin cancer." Anal canal cancer is more common in women, and anal margin cancer is more common in men.

Approximately 3,400 cases of anal cancer were diagnosed in the United States in 2000. Anal cancer accounts for 1.5% of the cancers of the digestive system. The average age at diagnosis is 62 years. Most anal cancers are squamous cell carcinomas.

Demographics

Women are much more likely than men to develop anal cancer. Anal cancer is more prevalent in Caucasians than other races.

Causes and symptoms

The previously held belief that anal cancer is caused by the chronic irritation associated with cracks (fissures),

hemorrhoids, and abnormal passageways (fistulae), is falling out of favor. It is now believed that most cases of anal cancer are caused by **human papilloma virus** (HPV), a sexually transmitted virus that can cause genital warts. Cancer is caused when the normal mechanisms that control cell growth become disturbed, causing the cells to grow continually without stopping. This may be the result of damage to the DNA in the cell or viral infection.

Symptoms of anal cancer may include:

- bleeding from the anus
- pain around the anus
- the sensation of anal pressure or a mass
- anal itching
- anal discharge
- straining to pass stool (rectal tenesmus)

Diagnosis

To diagnose anal cancer, the physician will first examine the skin of the anus and then will perform a **digital rectal examination** by inserting a greased, gloved finger into the rectum to feel for lumps. He or she will look for blood on the glove. If a lump is felt, a small sample of the lump will be removed (**biopsy**) through a small endoscope (flexible viewing instrument) to examine the tissue under a microscope. The biopsy may be performed using local anesthesia in the physician's office.

Although the diagnosis of anal cancer can be made by the examination alone, the cancer may be further evaluated by conducting other procedures. Endoscopic examinations of the anus (**anoscopy**) or rectum (proctoscopy) may be performed to see the tumor. **Endorectal ultrasound**, in which a wand-like ultrasound probe is inserted into the anus, enables the physician to determine how deep the tumor lies and whether or not nearby organs have been affected. Other possible diagnostic procedures include **x ray** and/or **computed tomography** (CT scan) to detect tumor spread (**metastasis**). It is common, however, for the cancer to be misdiagnosed at first as a benign lesion, such as a tissue lesion or hemorrhoid; due to this, treatment regimens may be delayed.

Treatment team

The treatment team for anal cancer may include a colorectal surgeon, gastroenterologist, oncologist, radiation oncologist, nurse oncologist, psychiatrist, psychological counselor, and social worker.

Clinical staging, treatments, and prognosis

Clinical staging

The American Joint Committee on Cancer and the Union Internationale Contra le Cancer developed a staging system for anal cancer. Anal cancer is categorized into five stages (0, I, II, III, and IV) which may be further subdivided (A and B) based on the depth or spread of cancerous tissue. This staging system does not apply to anal melanomas or **sarcomas**. Seventy-five percent of anal cancer patients have stage I or stage II disease. The stages of anal cancer are:

- Stage 0. Cancer has not spread below the limiting membrane of the first layer of anal tissue.
- Stage I. Cancer is 2 cm (approximately 0.75 in) or less in greatest dimension and has not spread anywhere else.
- Stage II. Cancer is between 2 and 5 cm in diameter and has spread beyond the topmost layer of tissue. There is no evidence of regional lymph node metastasis or distant metastasis.
- Stage IIIA. Cancer has spread to adjacent organs (e.g. vagina, bladder) or to the perirectal lymph nodes. Tumor may be of any size.
- Stage IIIB. Cancer has spread to nearby lymph nodes in the abdomen or groin or has spread to both adjacent organs and perirectal lymph nodes. Tumor may be of any size.
- Stage IV. Cancer has spread to distant abdominal lymph nodes or to distant organs in the body.

Treatments

The specific treatment depends on the stage of cancer, type of cancer, and the age and overall health of the patient. Anal cancer is most frequently treated with a combination of **radiation therapy** and **chemotherapy**.

Radiation therapy uses high-energy radiation from x rays and gamma rays to kill the cancer cells. Radiation given from a machine that is outside the body is called external radiation therapy. Radiation given internally is called internal radiation therapy or brachytherapy. Sometimes applicators containing radioactive compounds are placed directly into the cancerous lesion (interstitial radiation). The skin in the treated area may become red and dry and may take as long as a year to return to normal. **Fatigue**, upset stomach, **diarrhea**, and nausea are also common complaints of patients having radiation therapy. Women may develop vaginal narrowing (stenosis) caused by radiation therapy in the pelvic

area, which makes intercourse painful. Radiation may injure the anal sphincter and may cause anal ulcers and anal stenosis.

Chemotherapy uses anticancer drugs to kill the cancer cells. The drugs are given by mouth (orally) or intravenously. They enter the bloodstream and can travel to all parts of the body to kill cancer cells. Generally, a combination of drugs is given because it is more effective than a single drug in treating cancer. The side effects of chemotherapy are significant and include stomach upset, vomiting, appetite loss (**anorexia**), hair loss (**alopecia**), mouth sores, and fatigue. Women may experience vaginal sores, menstrual cycle changes, and premature menopause. There is also an increased chance of infections.

Surgery may occasionally be employed in the treatment of advanced or recurrent anal cancer. Associated lymph nodes may be surgically removed (lymphadenectomy) if they contain metastatic disease. Most frequently, the cancerous tissue is removed by a procedure called a local resection. In this procedure, the muscle (sphincter muscle) that opens and closes the anus to allow the passage of stool is usually preserved. Alternatively, an abdominoperineal resection is rarely performed surgery in which the anus and lower portion of the rectum are removed. This procedure involves cutting into the abdomen and the perineum, which lies between the anus and vagina in women or between the anus and scrotum in men. An opening is created so that stool can pass out of the body (**colostomy**) and into a special bag (colostomy bag) affixed to the skin. Because of the success of radiation therapy and chemotherapy, abdominoperineal resection is infrequently performed. It is reserved for certain patients with recurrent cancer and cancer that is not responding to more conservative treatments.

Prognosis

Anal cancer is a curable disease. Tumors that are located in the anal canal, are less than 2 cm in diameter, and are well-differentiated have a favorable prognosis. Anal cancer patients treated with radiation therapy and chemotherapy (without surgery) have a five-year survival rate of approximately 80%. In the United States, approximately 500 people die from anal cancer each year.

Anal cancer can spread locally and invade other pelvic organs such as the vagina, prostate gland, and bladder. Anal cancer that spreads through the bloodstream (hematogenous spread) most often strikes the liver and lungs.

Alternative and complementary therapies

Although alternative and complementary therapies are used by many cancer patients, very few controlled studies on the effectiveness of such therapies exist. Mind-body techniques such as prayer, biofeedback, visualization, meditation, and yoga have not demonstrated any effect in reducing cancer but can reduce stress and have been shown to lessen some of the side effects of cancer treatments.

Clinical studies of hydrazine sulfate found that it had no effect on cancer and actually worsened the health and well-being of the study subjects. Laetrile, or amygdalin, is often suggested as a cure for cancer and leukemia. No human or animal studies conducted in the last few decades have shown any benefit other than relief of some pain. Laetrile can, however, cause cyanide poisoning.

Shark cartilage is another popular treatment, but has not shown anticancer activity in a clinical setting. Although the results are mixed, clinical studies suggest that the hormone melatonin may increase the survival time and quality of life for cancer patients.

Vitamin E, broccoli, and ellagic acid (found in raspberries, strawberries, cranberries, etc.) may help to prevent colorectal cancer. Selenium, in safe doses, may delay the progression of cancer. Laboratory and animal studies suggest that curcumin, the active ingredient of turmeric, has anticancer activity. According to laboratory and animal studies, maitake mushrooms may boost the immune system. Some laboratory studies suggest that mistletoe has anticancer properties; however, clinical studies have not been conducted.

Coping with cancer treatment

The patient should consult their treatment team regarding any side effects or complications of treatment. Many of the side effects of chemotherapy can be relieved

KEY TERMS

Anal sphincter—The muscle located between the rectum and anus that opens and closes to allow the passage of stool.

Colostomy—An opening created in the skin that allows stool to pass out of the body. A colostomy is necessary when the anus and rectum are removed.

Human papilloma virus (HPV)—A sexually transmitted virus that causes genital and anal warts. It is associated with anal cancer and certain gynecologic cancers.

Stenosis—Narrowing of a passageway, such as radiation-induced narrowing of the vagina (vaginal stenosis) or anus (anal stenosis).

by medications. Vaginal stenosis can be prevented and treated by vaginal dilators, gentle douching, and sexual intercourse. A water-soluble lubricant may be used to make sexual intercourse more comfortable. Patients should consult a psychotherapist and/or join a support group to deal with the emotional consequences of cancer and its treatment.

Clinical trials

As of 2001, there was one active clinical trial that is specifically studying anal cancer. The trial (protocol RTOG-9811) is sponsored by the National Cancer Institute and is open to patients with stage II or III anal cancer. This study aims to compare the effectiveness of radiation therapy with either of two different pairs of chemotherapeutic agents (**fluorouracil** and mitomycin versus fluorouracil and **cisplatin**). There are other trials underway that include all types of **gastrointestinal cancers**, which may include anal cancer. Patients should consult with their treatment team to determine if they are candidates for any ongoing studies. The National Cancer Institute also provides information on **clinical trials**, and can be reached at (800) 4-CANCER or at <http://www.nci.nih.gov>.

Prevention

There is moderately strong evidence linking anal cancer with human immunodeficiency virus (AIDS) infection, cigarette smoking, or long term use of **corticosteroids**. Other factors that are strongly associated with the development of anal cancer include:

- Anogenital warts. Warts in and around the genitals and anus are found in 20% of women and heterosexual men and in 50% of homosexual men with anal cancer.
- Sexual activity. Having more than 10 sexual partners or being the recipient of anal intercourse increases the risk of developing anal cancer.
- Infections. Infection by sexually transmitted microbes, such as human papilloma virus HPV, herpesvirus, *Neisseria gonorrhoeae*, or *Chlamydia trachomatis*, places one at a higher risk of developing anal cancer.
- Gynecologic cancer. Women with a history of vaginal, vulvar, or **cervical cancer** are at risk of developing anal cancer. This risk is not due to therapeutic radiation exposure for gynecologic cancer.
- Chronic immunosuppression. The long-term use of drugs by organ transplant recipients to suppress the immune system increases the chance of developing a squamous **carcinoma**, such as anal cancer.

Because anal cancer is believed to be caused by HPV, like cervical cancer, it may be a preventable disease. Practicing safe-sex methods should help to prevent anal cancer. Persons who are at a high risk of developing anal cancer may benefit from routine screening by a physician.

QUESTIONS TO ASK THE DOCTOR

- What type of cancer do I have?
- What stage of cancer do I have?
- What is the 5 year survival rate for persons with this type and stage of cancer?
- Has the cancer spread?
- What are my treatment options?
- What are the risks and side effects of these treatments?
- What medications can I take to relieve treatment side effects?
- Are there any clinical studies underway that would be appropriate for me?
- Is surgery necessary?
- Will my anal sphincter be affected by surgery?
- Are there any alternatives to abdominoperineal resection?
- What effective alternative or complementary treatments are available for this type of cancer?
- How debilitating is the treatment? Will I be able to continue working?
- Are there any local support groups for anal cancer patients?
- What is the chance that the cancer will recur?
- Is there anything I can do to prevent recurrence?
- How often will I have follow-up examinations?

Special concerns

The effect of pelvic radiation therapy on fertility can be a concern for both men and women. The need for a colostomy raises many issues, including those related to **body image** and self esteem.

See also Fertility issues.

Resources

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American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) ACS-2345. <http://www.cancer.org>.

Cancer Research Institute, National Headquarters. 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

National Institutes of Health. National Cancer Institute. 9000 Rockville Pike, Bethesda, MD 20982. (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

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Belinda Rowland, Ph.D.

Anastrozole *see* **Aromatase inhibitors**

Anemia

Description

Anemia is characterized by an abnormally low number of red blood cells in the circulating blood. It frequently affects patients with cancer. In fact, in many cancer diagnoses such as **multiple myeloma** and **acute leukemia**, the presence of anemia may be what initially prompts a doctor to suspect an underlying tumor (neoplasm). Whether or not anemia develops depends on the type of cancer found, the treatment used, and the presence or absence of other underlying medical disorders.

Symptoms of malignancy-associated anemia may range from weakness, paleness, and **fatigue** to shortness of breath and increased heart rate. Symptoms of anemia can compromise a patient's ability to tolerate treatment, and may severely interfere with activities of daily living. Anemia may be particularly problematic in older individuals with cancer. The incidence and severity of anemia tends to increase as the cancer progresses.

Blood is comprised of three major cell types: white blood cells, which help the body fight infection; platelets, which help the blood to clot when necessary; and red blood cells, which transport oxygen from the lungs to the tissues in the body, and then transport carbon dioxide from those tissues back to the lungs. This exchange is enabled by the most important component of red blood cells—the protein called hemoglobin that binds easily to oxygen and carbon dioxide.

Red blood cells are produced in the bone marrow through a process called erythropoiesis. When the bone marrow functions normally, it continuously replaces red blood cells to maintain a normal level that allows for adequate oxygenation of the tissues. The hormone erythropoietin stimulates red blood cell production and sends a message to the bone marrow to increase production when oxygen levels in the body are low. This mechanism is often impaired in patients with cancer.

Causes

The causes of anemia are multiple, and often the factors act in conjunction with one another. Generally, anemia may result from a direct effect of a cancerous tumor, or from an indirect effect of the tumor. The cancer process may directly cause anemia through two main mechanisms: blood loss or bone marrow replacement. However, most cases of anemia in cancer patients result from the indirect effects of the cancer.

Direct effects of the tumor

Anemia is a frequent complication of cancers due to bleeding. Cancers of the head and neck, the gastrointestinal and genitourinary system, and the cervix are frequently associated with endogenous bleeding, or bleeding that occurs within the body. Bleeding occasionally develops within the tumor itself, particularly in **sarcomas**, melanomas, and ovarian and liver carcinomas.

A second direct cause of anemia in cancer is bone marrow replacement, which inhibits the body's ability to appropriately produce red blood cells. Certain cancers, such as acute leukemia, **lymphoma** and **myeloma**, directly suppress bone marrow function, thereby causing anemia. Other types of cancer, such as prostate or **breast cancer**, often spread to the bone marrow, inhibiting red blood cell production by actually replacing the bone marrow itself.

Indirect effects of the tumor

Anemia of chronic disease, also called anemia of malignancy, is the most common type of anemia seen in

individuals with cancer. It is a diagnosis made only after other possible causes are ruled out and if very specific conditions are met. The presence of low levels of iron coupled with normal levels of storage iron helps distinguish anemia of chronic disease from iron deficiency anemia. Factors that cause anemia of chronic disease are not entirely clear. However, it is believed that cytokines (non-antibody proteins) produced by the tumor reduce production of and impair responsiveness to erythropoietin. Typically, this type of anemia develops slowly. Rapid development of anemia may indicate another cause.

Treatments used to manage cancer have been implicated in the development of anemia in cancer patients. **Radiation therapy** to large areas of bone marrow, as in the hip area, may suppress bone marrow function and lead to anemia. **Chemotherapy** can also cause bone marrow suppression, and some drugs specifically target red blood cell production. Studies have shown that 10% to 40% of patients taking **cisplatin** develop significant anemia. Cisplatin, a chemotherapy drug with potentially toxic effects to the kidneys, is believed to reduce the production of the hormone erythropoietin in the kidneys. Although most treatment-induced bone marrow suppression is short term, there is some evidence to support the possibility of long-term problems with blood cell production.

Treatment can increase the risk of anemia in other ways. Chemotherapy, for example, causes bone marrow suppression that may reduce the immune system's ability to fight off opportunistic infection. The resulting infections can impact the bone marrow's functioning, possibly leading to the development of anemia.

Hemolytic anemia is a type of anemia in which the red blood cell has a shortened life span (normal life span is 90-120 days). Because the bone marrow is not able to compensate by producing more red blood cells, anemia results. Abnormalities in the red blood cells may originate in the body (intrinsic) or may be caused by environmental factors such as auto-antibodies to red blood cells or damage from chemotherapy.

Although one factor may have a greater influence, it is important to realize that several factors may be causing anemia. For example, approximately 70% of patients with multiple myeloma are anemic at the time of diagnosis. Anemia in these cases is caused by a combination of mechanisms including bone marrow replacement with cancer cells, bone marrow suppression from chemotherapy, and impaired production of erythropoietin.

Treatments

Treatment of the anemia is directed at the underlying cause. In many cases, treating or removing the cancer corrects the red blood cell deficit. Management of autoimmune hemolytic anemia, which can be associated with **chronic lymphocytic leukemia**, may range from the administration of **corticosteroids** to the surgical removal of the spleen. More commonly, cancer-related anemias are treated with blood transfusions and/or a drug called epoetin alfa.

Blood transfusions

Blood transfusions have been the principle treatment for anemia for many years. Until the 1960s, only whole blood was given. Then, methods of separating whole blood were devised, allowing only particular components, such as platelets, red blood cells, or plasma, to be transfused.

Blood transfusions are not without risk, and must be used carefully. Many patients react to the white blood cell antigens by developing a **fever**. This is so common that patients are routinely premedicated to prevent fever from developing. Individuals with long-term transfusion needs, such as patients with leukemia, may be given blood products with a reduced number of white blood cells to reduce the risk of sensitization to transfused blood.

Cytomegalovirus (CMV) is a virus that may be present in blood products. Although it has no effect on individuals with normally functioning immune systems, cancer patients often have a diminished ability to fight infection. These patients may be at risk for CMV if they are CMV negative and receive CMV-positive blood.

Transfusion-associated graft-versus-host disease (TA-GvHD) is another risk factor associated with blood transfusions in cancer patients. Although it is very rare, it is often fatal. With TA-GvHD, the patient's immune system does not recognize the white blood cells in the donor blood as "nonself." The donor white blood cells, however, recognize the patient as "nonself," and an immune-mediated reaction ensues. To prevent this reaction in at-risk patients, blood may be irradiated prior to transfusion.

Epoetin alfa

As mentioned previously, erythropoietin is a protein produced in the kidneys that stimulates red blood cell production. Using DNA technology, this hormone has been replicated to create the drug epoetin alfa for the treatment of anemia in select cancer patients. (The drug is also called **erythropoietin**.) The use of this drug in the cancer setting has shown great promise, both in the treatment of cancer-related anemia, and in the reduction in the need for blood transfusion.

However, epoetin alfa therapy is not advisable for everyone. This drug is not recommended for use in can-

KEY TERMS

Cytokines—Non-antibody proteins released by a group of cells that act as mediators in immune response.

Cytomegalovirus (CMV)—A virus sometimes present in blood products.

Erythropoiesis—The process in which red blood cells are produced in the bone marrow.

Erythropoietin—A hormone produced by the kidneys that stimulates the production of red blood cells in a process called erythropoiesis.

Hematocrit—The volume percentage of red blood cells in whole blood.

Hemoglobin—A protein in red blood cells that transports oxygen to tissues.

cer-related anemia caused by bleeding, hemolysis, or iron deficiencies. Nor is it recommended for patients with hypertension or albumin sensitivity. Because no human studies are available to determine its effect on a fetus, women taking epoetin alfa should take measures to prevent pregnancy.

Cancer patients with anemia who are undergoing chemotherapy may benefit from this drug. Studies have shown an increased hematocrit (the volume percentage of red blood cells in whole blood) level and a decreased need for blood transfusions after the first month of therapy in this population. Epoetin alfa may be injected up to three times a week, and throughout therapy, blood cell counts are monitored closely. In 2004, it was reported that a form of the drug could be injected only once every two weeks in some cancer patients with the same effect, making its use more convenient.

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Angiogenesis inhibitors

Definition

Angiogenesis inhibitors are medicines that stop the formation of new blood vessels in and around cancerous tumors.

Description

Angiogenesis inhibitors are a group of medicines that prevent the formation of tiny new blood vessels to the area of cancerous tumors. Angiogenesis refers to the ability of cancer cells to form new blood vessels that invade the tumor and other surrounding areas. Tumors need a blood supply to nourish the cancer cells, and as tumors grow they must constantly form new blood vessels. These blood vessels are also used by the cancer cells to metastasize or spread the cancerous cells from one area to the next. Angiogenesis inhibitors are important because the scientific theory is that if one can remove and/or prevent the formation of new blood vessels in the tumors, the cancer cells will not be able to grow any further. This could cause the tumors to stay the same size or shrink. In addition, it may be possible to prevent the tumors from spreading by cutting off their ability to invade other surrounding areas through these newly formed blood vessels. There are a few drugs today thought to work as angiogenesis inhibitors, such as **thalidomide**. Additional agents being studied in ongoing oncology **clinical trials**.

Nancy J. Beaulieu, RPh., BCOP

Angiography

Definition

Angiography is the x-ray study of the blood vessels. An angiogram uses a radiopaque substance, or dye, to make the blood vessels visible under **x ray**. Arteriography is a type of angiography that involves the study of the arteries.

Purpose

Angiography is used to detect abnormalities or blockages in the blood vessels (called occlusions) throughout the circulatory system and in some organs. The procedure is commonly used to: identify atherosclerosis; diagnose heart disease; evaluate kidney function and detect kidney cysts or tumors; detect an aneurysm (an abnormal bulge of an artery that can rupture and lead to hemorrhage), tumor, blood clot, or arteriovenous malformations (abnormal tangles of arteries and veins) in the brain; and to diagnose problems with the retina of the eye. It is also used to give surgeons an accurate "map" of the heart prior to open-heart surgery, or of the brain prior to neurosurgery.

Precautions

Patients with kidney disease or injury may suffer further kidney damage from the contrast mediums used for angiography. Patients who have blood clotting problems, have a known allergy to contrast mediums, or are allergic to iodine, a component of some contrast mediums, may also not be suitable candidates for an angiography procedure. Because x rays carry risks of ionizing radiation exposure to the fetus, pregnant women are also advised to avoid this procedure.

Description

Angiography is usually performed at a hospital by a trained radiologist and assisting technician or nurse. It takes place in an x-ray or fluoroscopy suite, and for most types of angiograms, the patient's vital signs will be monitored throughout the procedure.

Angiography requires the injection of a contrast dye that makes the blood vessels visible to x ray. Tissues such as bones and blood vessels absorb x rays as they pass through the body. They show up with a clear, white outline when captured on film. The dye is injected through a procedure known as arterial puncture. The puncture is usually made in the groin area, inside elbow, or neck. The site is cleaned with an antiseptic agent and injected with a local anesthetic. First, a small incision is made in the skin to help the needle pass. A needle containing an inner wire called a stylet is inserted through the skin into the artery. When the radiologist has punctured the artery with the needle, the stylet is removed and replaced with another long wire called a guide wire. It is normal for blood to spout out of the needle before the guide wire is inserted.

The guide wire is fed through the outer needle into the artery and to the area that requires angiographic study. A fluoroscopic screen that displays a view of the patient's vascular system is used to pilot the wire to the correct location. Once it is in position, the needle is removed and a catheter is slid over the length of the guide wire until it to reaches the area of study. The guide wire is removed and the catheter is left in place in preparation for the injection of the contrast medium, or dye.

Depending on the type of angiography procedure being performed, the contrast medium is either injected by hand with a syringe or is mechanically injected with an automatic injector connected to the catheter. An automatic injector is used frequently because it is able to propel a large volume of dye very quickly to the angiogram site. The patient is warned that the injection will start, and instructed to remain very still. The injection causes some mild to moderate discomfort. Possible side effects or reactions include headache, dizziness, irregular heartbeat, nausea, warmth, burning sensation, and chest pain, but they usually last only momentarily. To view the area of study from different angles or perspectives, the patient may be asked to change positions several times, and subsequent dye injections may be administered. During any injection, the patient or the camera may move.

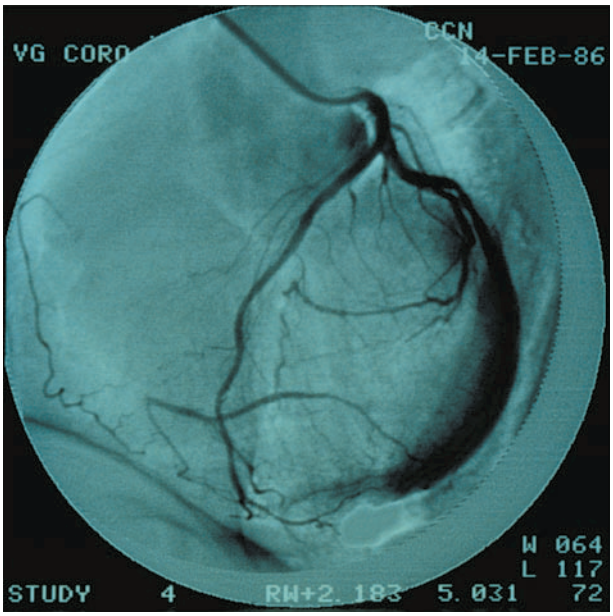
Throughout the dye injection procedure, x-ray pictures and/or fluoroscopic pictures (moving x rays) will be taken. Because of the high pressure of arterial blood flow, the dye will dissipate through the patient's system quickly, so pictures must be taken in rapid succession. An automatic film changer is used because the manual changing of x-ray plates can eat up valuable time.

Once the x rays are complete, the catheter is slowly and carefully removed from the patient. Pressure is applied to the site with a sandbag or other weight for 10 to 20 minutes in order for clotting to take place and the arterial puncture to reseal itself. A pressure bandage is then applied.

Most angiograms follow the general procedures outlined above, but vary slightly depending on the area of the vascular system being studied. In addition to x rays, technological advances have allowed physicians to use other diagnostic tools for angiography, such as **computed tomography** (CT) scans and **magnetic resonance imaging** (MRI). A variety of common angiography procedures are outlined below:

Cerebral angiography

Cerebral angiography is used to detect aneurysms, blood clots, and other vascular irregularities in the brain. The catheter is inserted into the femoral artery (the main artery of the thigh) or the carotid artery in the neck, and



An angiogram of a coronary artery. *(Copyright CNRI/Phototake NYC. Reproduced by permission.)*

the injected contrast medium travels through the blood vessels of the brain. Patients frequently experience headache, warmth, or a burning sensation in the head or neck during the injection portion of the procedure. A cerebral angiogram takes two to four hours to complete.

Coronary angiography

Coronary angiography is administered by a cardiologist with training in radiology or, occasionally, by a radiologist. The arterial puncture is typically given in the femoral artery, and the cardiologist uses a guide wire and catheter to perform a contrast injection and x-ray series on the coronary arteries (arteries that supply the heart with oxygenated blood). The catheter may also be placed in the left ventricle to examine the mitral and aortic valves of the heart. If the cardiologist requires a view of the right ventricle of the heart or of the tricuspid or pulmonic valves, the catheter will be inserted through a large vein and guided into the right ventricle. The catheter also serves the purpose of monitoring blood pressures in these different locations inside the heart. The angiogram procedure takes several hours, depending on the complexity of the procedure. Some cardiologists prefer to use a compbination of CT and x-ray angiography to study the heart.

Pulmonary angiography

Pulmonary, or lung, angiography is performed to evaluate blood circulation to the lungs. It is also considered the most accurate diagnostic test for detecting a pulmonary embolism, although some physicians prefer CT or MRI scans because they are less invasive. New technology has improved the accuracy of these alternative methods. The procedure differs from cerebral and coronary angiograms in that the guide wire and catheter are inserted into a vein instead of an artery, and are guided up through the chambers of the heart and into the pulmonary artery. Throughout the procedure, the patient's vital signs are monitored to ensure that the catheter does not cause arrhythmias, or irregular heartbeats. The contrast medium is then injected into the pulmonary artery where it circulates through the lung capillaries. The test typically takes up to 90 minutes.

Kidney angiography

Patients with chronic renal disease or injury can suffer further damage to their kidneys from the contrast medium used in a kidney angiogram, yet they often require the test to evaluate kidney function. These patients should be well-hydrated with a intravenous saline drip before the procedure, and may benefit from available medications (e.g., dopamine) that help to protect the kidney from further injury due to contrast agents. During a kidney angiogram, the guide wire and catheter are inserted into the femoral artery in the groin area and advanced through the abdominal aorta, the main artery in the abdomen, and into the renal arteries. The procedure will take approximately one hour.

Fluorescein angiography

Fluorescein angiography is used to diagnose retinal problems and circulatory disorders. It is typically conducted as an outpatient procedure. The patient's pupils are dilated with eye drops and he rests his chin and forehead against a bracing apparatus to keep it still. Sodium fluorescein dye is then injected with a syringe into a vein in the patient's arm. The dye will travel through the patient's body and into the blood vessels of the eye. The procedure does not require x rays. Instead, a rapid series of close-up photographs of the patient's eyes are taken, one set immediately after the dye is injected, and a second set approximately 20 minutes later once the dye has moved through the patient's vascular system. The entire procedure takes up to one hour.

Celiac and mesenteric angiography

Celiac and mesenteric angiography involves x-ray exploration of the celiac and mesenteric arteries, arterial branches of the abdominal aorta that supply blood to the abdomen and digestive system. The test is commonly used to detect aneurysm, thrombosis, and signs of ischemia in the celiac and mesenteric arteries, and to locate

KEY TERMS

Arteriosclerosis—A chronic condition characterized by thickening and hardening of the arteries and the buildup of plaque on the arterial walls. Arteriosclerosis can slow or impair blood circulation.

Carotid artery—An artery located in the neck.

Catheter—A long, thin, flexible tube used in angiography to inject contrast material into the arteries.

Cirrhosis—A condition characterized by the destruction of healthy liver tissue. A cirrhotic liver is scarred and cannot break down the proteins in the bloodstream. Cirrhosis is associated with portal hypertension.

Computed tomography (CT)—A non-invasive diagnostic tool radiologists may use instead of x-ray angiography.

Embolism—A blood clot, air bubble, or clot of foreign material that travels and blocks the flow of blood in an artery. When blood supply to a tissue or organ is blocked by an embolism, infarction, or death of the tissue the artery feeds, occurs. Without immediate and appropriate treatment, an embolism can be fatal.

Femoral artery—An artery located in the groin area that is the most frequently accessed site for arterial puncture in angiography.

Fluorescein dye—An orange dye used to illuminate the blood vessels of the retina in fluorescein angiography.

Fluoroscopic screen—A fluorescent screen which displays moving x rays of the body. Fluoroscopy allows the radiologist to visualize the guide wire and catheter he is moving through the patient's artery.

Guide wire—A wire that is inserted into an artery to guide a catheter to a certain location in the body.

Ischemia—A lack of normal blood supply to a organ or body part because of blockages or constriction of the blood vessels.

Magnetic resonance imaging (MRI)—A non-invasive diagnostic tool radiologists may use instead of x-ray angiography. MRI scans use magnetic waves to create a picture of structures in the body.

Necrosis—Cellular or tissue death; skin necrosis may be caused by multiple, consecutive doses of radiation from fluoroscopic or x-ray procedures.

Plaque—Fatty material that is deposited on the inside of the arterial wall.

Portal hypertension—A condition caused by cirrhosis of the liver. It is characterized by impaired or reversed blood flow from the portal vein to the liver, an enlarged spleen, and dilated veins in the esophagus and stomach.

Portal vein thrombosis—The development of a blood clot in the vein that brings blood into the liver. Untreated portal vein thrombosis causes portal hypertension.

the source of gastrointestinal bleeding. It is also used in the diagnosis of a number of conditions, including portal hypertension and cirrhosis. The procedure can take up to three hours, depending on the number of blood vessels studied.

Splenoportography

A splenoportograph is a variation of an angiogram that involves the injection of contrast medium directly into the spleen to view the splenic and portal veins. It is used to diagnose blockages in the splenic vein and portal vein thrombosis and to assess the strength and location of the vascular system prior to liver transplantation.

Most angiography procedures are typically paid for by major medical insurance. Patients should check with their individual insurance plans to determine their coverage.

Preparation

Patients undergoing an angiogram are advised to stop eating and drinking eight hours prior to the procedure. They must remove all jewelry before the procedure and change into a hospital gown. If the arterial puncture is to be made in the armpit or groin area, shaving may be required. A sedative may be administered to relax the patient for the procedure. An IV line will also be inserted into a vein in the patient's arm before the procedure begins in case medication or blood products are required during the angiogram.

Prior to the angiography procedure, patients will be briefed on the details of the test, the benefits and risks,

and the possible complications involved, and asked to sign an informed consent form.

Aftercare

Because life-threatening internal bleeding is a possible complication of an arterial puncture, an overnight stay in the hospital is sometimes recommended following an angiography procedure, particularly with cerebral and coronary angiograms. If the procedure is performed on an outpatient basis, the patient is typically kept under close observation for a period of six to twelve hours before being released. If the arterial puncture was performed in the femoral artery, the patient will be instructed to keep his leg straight and relatively immobile during the observation period. The patient's blood pressure and vital signs will be monitored and the puncture site observed closely. Pain medication may be prescribed if the patient is experiencing discomfort from the puncture, and a cold pack is applied to the site to reduce swelling. It is normal for the puncture site to be sore and bruised for several weeks. The patient may also develop a hematoma, a hard mass created by the blood vessels broken during the procedure. Hematomas should be watched carefully, as they may indicate continued bleeding of the arterial puncture site. Patients may be given intravenous fluids and may experience a frequent need to urinate due to the x-ray dye.

Angiography patients are also advised to enjoy a few days of rest and relaxation after the procedure in order to avoid placing any undue stress on the arterial puncture. Patients who experience continued bleeding or abnormal swelling of the puncture site, sudden dizziness, chest pains, chills, nausea, headaches, or numbness in the days following an angiography procedure should seek medical attention immediately.

Patients undergoing a fluorescein angiography should not drive or expose their eyes to direct sunlight for 12 hours following the procedure.

Risks

Because angiography involves puncturing an artery, internal bleeding or hemorrhage are possible complications of the test. As with any invasive procedure, infection of the puncture site or bloodstream is also a risk, but this is rare.

A stroke or heart attack may be triggered by an angiogram if blood clots or plaque on the inside of the arterial wall are dislodged by the catheter and form a blockage in the blood vessels or artery. The heart may also become irritated by the movement of the catheter through its chambers during pulmonary and coronary angiography procedures, and arrhythmias may develop.

Patients who develop an allergic reaction to the contrast medium used in angiography may experience a variety of symptoms, including swelling, difficulty breathing, heart failure, or a sudden drop in blood pressure. If the patient is aware of the allergy before the test is administered, certain medications can be administered at that time to counteract the reaction.

Angiography involves minor exposure to radiation through the x rays and fluoroscopic guidance used in the procedure. Unless the patient is pregnant, or multiple radiological or fluoroscopic studies are required, the small dose of radiation incurred during a single procedure poses little risk. However, multiple studies requiring fluoroscopic exposure that are conducted in a short time period have been known to cause skin necrosis (cell death) in some individuals. This risk can be minimized by careful monitoring and documentation of cumulative radiation doses administered to these patients.

Normal results

The results of an angiogram or arteriogram depend on the artery or organ system being examined. Generally, test results should display a normal and unimpeded flow of blood through the vascular system. Fluorescein angiography should result in no leakage of fluorescein dye through the retinal blood vessels.

Abnormal results

Abnormal results of an angiography may display a restricted blood vessel or arterial blood flow (ischemia) or an irregular placement or location of blood vessels. The results of an angiography vary widely by the type of procedure performed, and should be interpreted and explained to the patient by a trained radiologist.

QUESTIONS TO ASK THE DOCTOR

- Did you see any abnormalities?
- How long will I need to stay in the hospital? How many days until I can resume normal activities?
- When can I resume any medications that were stopped?
- What future care will I need?

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Paula Anne Ford-Martin

Anorexia

Definition

Anorexia is characterized by a loss of appetite or lack of desire to eat.

Description

Anorexia is common in cancer patients with reported incidence between 15% and 40%. Primary anorexia is especially prevalent in patients with advanced malignancy, and is frequently a side effect of cancer treatments. Sometimes, early symptoms may remain undiagnosed, or will be masked by a more generalized wasting of the body from chronic disease, known as cachexia.

When patients experience appetite loss, decreased energy consumption will subsequently lead to **weight loss**. When inadequate calories are consumed, the body may become weaker and less able to tolerate cancer therapies. As body weight decreases, cachexia sets in, and a general failure to thrive may make it more difficult to fight off illness and infection. A poor response to cancer treatments, reduced quality of life, and death may result from substantial weight loss. The spiraling effect of a patient's reluctance to eat is a source of frequent anxiety for caregivers. Weight loss due to anorexia may be temporary or may continue at a life-threatening pace if the patient continues to consume inadequate energy to sustain bodyweight.

Causes

It is normal for a patient to consume less energy when not as active. It is also natural to lose interest in food when individuals are seriously ill. However, it is essential in anorexic patients to consider whether the loss of appetite is the result of a natural disinterest in eating (primary anorexia), or is due to some reversible cause (secondary anorexia).

Secondary anorexia may be a result of:

- nausea with or without fear of vomiting after food consumption
- fatigue
- constipation
- sores in the mouth or mouth pain
- candidiasis
- unappetizing food or change in food preference due to cancer-related treatments
- **depression**
- odors in the environment, or heightened sensitivity to odors as a result of cancer-related treatments
- early satiation
- metabolic causes such as **hypercalcemia** and uremia
- **radiation therapy** or **chemotherapy**
- drugs such as **antibiotics** or drugs that can cause nausea

Special concerns

In order to allow normal tissue repair following aggressive cancer therapies, patients require adequate energy and macronutrients in the form of protein, carbohydrates, and fat. Inadequate consumption of food and/or poor nutrition may impair the ability of a patient to tolerate a specific therapy. If a low tolerance to therapy necessitates a decrease in dose, the therapy's effectiveness could be compromised. Wound healing may also be impaired with poor nutrition and inadequate energy intake.

Individuals who experience pain, nausea, or **diarrhea** due to the side effects of radiation and chemotherapy may want to discuss treatments options with their doctor to ease these side effects.

Treatments

Dietary tips for managing anorexia

- Serve food when the patient is hungry. A microwave oven often helps.
- Have the patient eat small meals every one to two hours, or time meals corresponding to when the patient feels best (typically early in the day).
- If only a little food is consumed by the patient, it should ideally be high in protein and calories. Avoid empty calories (i.e. foods without protein and nutrients).
- Add extra calories and protein to foods with the use of butter, skim milk powder, commercially prepared protein powder, honey, or brown sugar.
- Try to tempt the patient with tiny portions on small plates.
- Serve food in an attractive manner.
- Food is more likely to be eaten if it is served at frequent intervals unrelated to standard meal times.
- Avoid strong aromas if the patient finds them bothersome.
- Avoid liquids with meals to decrease problems of early satiety
- A small alcoholic drink of the patient's choice may help unless contraindicated.
- Consider flavors, consistency and quantity of food when preparing meals.
- Encourage eating with friends or family members; a meal in a social setting may help the patient to eat.
- Stimulate appetite with light exercise.
- Treat any underlying cause and, if a particular drug appears to be the cause, modify drug regimen.
- Have the patient take medications with high-calories fluids, i.e. commercial liquid supplements unless medication necessitates an empty stomach.

Often, patients may experience difficulty with eating due to upper gastrointestinal blockage such as problems with swallowing, esophageal narrowing, tumor, stomach weakness, paralysis, or other conditions that preclude normal food intake. In those circumstances, enteral nutrition may be administered through a tube into the gastrointestinal tract via the nose, or through surgically placed tubes into the stomach or intestines. If the gastrointestinal tract is working and will not be affected by the cancer treatments, then enteral support by feeding directly into the gut is preferable. Parenteral nutrition (most often an infusion into a vein) can be used if the gut is not functioning properly or if there are other reasons that prevent enteral feeding.

KEY TERMS

Anorexia—A condition frequently observed in cancer patients characterized by a loss of appetite or desire to eat.

Cancer—A term for diseases in which abnormal cells divide without control. Cancer cells can invade nearby tissues and can spread through the bloodstream and lymphatic system to other parts of the body.

Candidiasis—A yeast-like fungal infection occuring on the skin or mucous membranes, i.e. mouth.

Chemotherapy—Chemotherapy kills cancer cells using drugs taken orally or by needle in a vein or muscle. It is referred to as a systemic treatment due to fact that it travels through the bloodstream and kills cancer cells outside the small intestine.

Hypercalcemia— A high calcium blood concentration above 10.5 milligrams per deciliter of blood. Increased gastrointestinal tract absorption or increased intake of calcium may lead to hypercalcemia.

Malignant (also malignancy)— Meaning cancerous; a tumor or growth that often destroys surrounding tissue and spreads to other parts of the body.

Radiation therapy—Also called radiotherapy; uses high-energy x-rays to kill cancer cells.

Satiation—A feeling of fullness or satisfaction during or after food intake.

Uremia—An excess of nitrogenous substances in the blood that are toxic and usually excreted by the kidneys.

An appetite stimulant may be given such as **megestrol acetate** or **dexamethasone**. In **clinical trials**, both these medications appear to have similar and effective appetite stimulating effects with megestrol acetate having a slightly better toxicity profile. **Fluoxymesterone** has shown inferior efficacy and an unfavorable toxicity profile.

Alternative and complementary therapies

Depression may affect approximately 15-25% of cancer patients, particularly if the prognosis for recovery is poor. If anorexia is due to depression, there are antidepressant choices available through a physician. Counseling may be also be sought through a psychologist or psychiatrist to deal with depression.

St. John's Wort has been used as a herbal remedy for treatment of depression, but it and prescription antidepressants is a dangerous combination that may cause symptoms such as nausea, weakness, and may cause one to become incoherent. It is important to check with a dietitian or doctor before taking nutritional supplements or alternative therapies because they may interfere with cancer medications or treatments.

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The National Cancer Institute (NCI). For information contact the Public Inquiries Office: Building, 31, Room 10A31, 31 Center Drive, MSC 2580, Betheseda, MD 20892-2580 USA. (301) 435-3848, 1-800-4-CANCER. <http://cancer.gov/publications>, <http://cancernet.nci.nih.gov>.

National Center for Complementary and Alternative Medicine (NCCAM). 31 Center Dr., Room #5B-58, Bethesda, MD 20892-2182. (800) NIH-NCAM, Fax (301) 495-4957. <http://nccam.nih.gov>.

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Anoscopy

Definition

Anoscopy is a diagnostic procedure that allows a gastroenterologist or other physician to visually examine the rectum, anus, and anal canal.

KEY TERMS

Anorectal—Pertaining to the anus and rectum

Anus—The opening of the rectum through which feces leave the body

Rectum—The portion of the large intestine where feces is stored before leaving the body

Purpose

Doctors use anoscopy to diagnose **rectal cancer** and cancer of the anus. This procedure can also help the doctor:

- detect any lesions that could not be felt during a digital examination
- determine whether squamous cell carcinomas involving lymph nodes in or near the groin (inguinal lymph nodes) originated in the genital area or in or near the anus or rectum
- confirm the source of malignancies that have spread to the anorectal area from other parts of the body

Doctors also perform anoscopy to determine whether a patient has hemorrhoids or anal:

- growths or nodules (polyps)
- ulcer-like grooves (fissures)
- inflammation
- infection

Description

After removing underwear, the patient bends forward over the examining table or lies on one side with knees drawn up to the chest. The doctor performs a digital examination to make sure no tumor or other abnormality will obstruct the passage of a slender lubricated tube (anoscope). As the doctor gently guides the anoscope a few inches into the rectum, the patient is told to bear down as though having a bowel movement, then relax.

By tensing and relaxing, the patient makes it easier for the doctor to insert the anoscope, and discover growths in the lining of the rectum that could not be detected during the digital examination.

Directing a light into the anoscope gives the doctor a clear view of any tears or other irregularities in the lower anus or rectum. A doctor who suspects that a patient may have cancer will remove tissue for **biopsy** in the course of this procedure.

Slowly withdrawing the anoscope allows the doctor to thoroughly inspect the entire anal canal. As the procedure is being performed, the doctor explains what is happening, and why the patient feels pressure.

Removing tissue samples for biopsy can pinch, but anoscopy does not usually cause pain. Patients do experience the sensation of needing to have a bowel movement.

Preparation

The rectum should be emptied of fecal matter (stool) before the procedure is performed. The doctor may suggest using:

- a laxative,
- an enema,
- or some other preparationto clear the rectum.

Aftercare

As soon as the procedure is completed, the doctor can tell the patient whether the results are normal or abnormal, and the patient can resume normal activities.

Risks

Removing tissue for biopsy may cause a little bleeding and some slight pain, but there are no significant risks associated with anoscopy.

Normal results

A normal anoscopy reveals no evidence of:

- tumor
- tissue irregularities
- polyps
- fissures
- hemorrhoids
- inflammation
- infectionor other abnormalities. The size, color, and shape of the anal canal look like they should.

Abnormal results

Abnormal results of anoscopy can indicate the presence of:

- cancer
- abscesses
- polyps
- inflammation

QUESTIONS TO ASK THE DOCTOR

- Why do you want me to have anoscopy?
- How long will this procedure take?
- What will the results of this test tell you?

- infection
- fissures
- hemorrhoids

See also Anal cancer; Digital rectal examination.

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Maureen Haggerty

Antiandrogens

Definition

Antiandrogens, including flutamide (brand name Eulexin or Euflex), bicalutamide (brand name Casodex), and nilutamide (brand name Nilandron), are medicines used in the treatment of advanced **prostate cancer**.

Purpose

Antiandrogens are approved by the Food and Drug Administration (FDA) for the treatment of prostate gland cancer that has spread to other areas of the body.

Purpose

Antiandrogen therapy stops or blocks the effect androgen presence has on tumor cells of the prostate. Antiandrogens are combined with either surgery or drug therapy that shuts down male hormone production. The common drugs used with antiandrogens are known as luteinizing hormone releasing hormone (LHRH) agonists, referred to by the brand names Lupron or

Zoladex. The LHRH agonists produce side effects that the antiandrogens can keep under control; thus the combination of the two types of agents has improved survival in prostate cancer patients.

Newer trends in antiandrogen therapy include intermittent treatment with the drugs rather than continuous dosage; and antiandrogen monotherapy for patients whose cancer is still localized. Monotherapy means that the patient is given only the antiandrogen drugs without any LHRH agonists. As of late 2003, however, antiandrogen monotherapy is considered an investigational treatment.

Description

Antiandrogens will not cure prostate cancer, but they will help improve some of the disease's symptoms. They may also increase survival time.

Androgens are made naturally in the body and include the hormone **testosterone** and its related compound, dihydrotestosterone. The testes produce the majority of testosterone. The adrenal glands also produce androgens in smaller amounts. Prostate cancer cells grow due to normal levels of androgens produced by the body. Some patients have prostate tumors that are extra-sensitive to androgens in the blood. The androgens attach to receptors on the tumor cells and send a signal to the tumor cells causing them to grow and multiply. Antiandrogen drugs block the receptors on the prostate cancer cell that are sensitive to the androgen hormones. By blocking these receptors, known as androgen-receptors, the cancer cells cannot be instructed to grow and multiply. Antiandrogens also cause the body to decrease production of androgens and, as a result, their effects.

Recommended dosage

Flutamide

Flutamide is an oral capsule dosed at 250 mg three times a day in combination with the LHRH agonist or surgical removal of the testis.

Bicalutamide

Bicalutamide is an oral tablet dosed at 50 mg once a day in combination with the LHRH agonist. The dose may need to be decreased in patients with decreased liver function.

Nilutamide

Nilutamide is an oral tablet dosed at 300 mg once a day for 30 days then 150 mg once a day in combination with surgical removal of the testis.

KEY TERMS

Adrenal gland—Small organ located above the kidneys that produce hormones.

Food and Drug Administration—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives approval to pharmaceutical companies for commercial marketing of their products

LHRH agonists—Luteinizing hormone-releasing hormone drugs that initially stimulate the testes to make and release testosterone. With time, as the amount of testosterone in the blood rises, it stops the production of luteinizing hormone, which results in stopping overall production of testosterone.

Monotherapy—Treatment of a disease or disorder with the use of a single drug.

Osteoporosis—A condition in which the loss of minerals from the bone leads to fractures after minor trauma. Osteoporosis can develop in men taking antiandrogen drugs for prostate cancer.

Precautions

Although antiandrogens are primarily given to men, women taking them should avoid pregnancy. Antiandrogens block the male hormone called testosterone and, as a result, can adversely affect the developing fetus. Blood counts will be monitored while on antiandrogen therapy.

Side effects

The most common side effects from all antiandrogens are due to the decreased levels of hormones. These commonly include hot flashes, loss of sex drive, tiredness, and impotence (the inability of males to have sexual intercourse).

Antiandrogens can also cause mild nausea, vomiting, **diarrhea**, loss of appetite, enlarged breasts or breast tenderness, skin reactions, muscle aches, liver problems, blood in the urine and generalized pain and decrease in blood counts. Nilutamide may cause visual disturbances, with patients having difficulty with the dark. Rarely, lung problems have occurred due to nilutamide or bicalutamide, including cough and shortness of breath.

These drugs must be used with caution in patients who are receiving the blood-thinning drug Coumadin (**warfarin**) or the drugs **phenytoin** and theophylline. Combining these drugs with antiandrogen therapy may increase the effects or side effects of these agents.

Another potentially troublesome side effect of antiandrogens is bone loss. Men who are taking these drugs are at increased risk of osteoporosis and consequent bone fractures. Doctors are now recommending that male patients taking these drugs should have a baseline assessment of their bone mineral density, and should be given zoledronic acid (Zometa) if there is evidence of serious bone loss.

Interactions

Patients should tell their doctors if they have a known allergic reaction to antiandrogens or any other medications or substances, such as foods and preservatives. Before taking any new medications, including nonprescription medications, **vitamins**, and herbal medications, the patients should notify their doctors.

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Antibiotics

Definition

Antibiotics are drugs that are used to treat infections caused by bacteria and other organisms, including protozoa, parasites, and fungi.

Purpose

Many treatments for cancer destroy disease-fighting white blood cells, thereby reducing the body's ability to fight infection. For example, bladder, pulmonary, and urinary tract infections may occur with **chemotherapy**. Single-celled organisms called protozoa are rarely a problem for healthy individuals. However, they can cause serious infections in individuals with low white blood cell counts. Because of the dangers that infections present for cancer patients, antibiotic treatment often is initiated before the exact nature of the infection has been determined; instead, the choice of antibiotic may depend on the site of the infection and the organism that is likely to be the cause. Often, an antibiotic that kills a broad spectrum of bacteria is chosen and several antibiotics may be used together.

Description

The common antibiotics that are used during cancer treatment include:

- Atovaquone (Mapren): antiprotozoal drug used to prevent and treat a very serious type of **pneumonia** called *Pneumocystis carinii* pneumonia (PCP), in individuals who experience serious side effects with SMZ-TMP (Sulfamethoxazole/Trimethoprim, brand name Bactrim).
- Aztreonam (Azactam): monobactam antibiotic used to treat gram-negative bacterial infections of the urinary and lower respiratory tracts and the female organs, and infections that are present throughout the body (systemic infections or septicemia).
- Cefepime (Maxipime), ceftazidime (Ceptaz, Fortaz, Tazicef, Tazidime), and ceftriaxone sodium (Rocephin): members of a group of antibiotics called cephalosporins used to treat bacterial infections of the urinary and lower respiratory tracts, and infections of the skin, bones, joints, pelvis, and abdomen.
- Ciprofloxacin (Cipro): fluoroquinolone antibiotic used to treat certain gram-negative and gram-positive bacteria and some mycobacteria.
- Clindamycin phosphate (Cleocin): used to treat gram-positive and gram-negative bacterial infections and, in individuals who are allergic to sulfadiazine, toxoplasmosis caused by a parasitic protozoa.

- Gentamicin (gentamycin) sulfate (generic name product, Garamycin, G-Mycin, Jenamicin): aminoglycoside antibiotic used to treat serious infections by many gram-negative bacteria that cannot be treated with other medicines.
- Metronidazole hydrochloride (Flagyl, Metric 21, Metro I.V., Protostat): used for anaerobic bacteria and protozoa.
- Pentamidine (generic name product, Pentam 300): used to treat PCP if serious side effects develop with SMZ-TMP.
- Pyrimethamine (Daraprim): antiprotozoal medicine used together with sulfadiazine to treat toxoplasmosis; or in combination with other medicines for treating mild to moderate PCP, in individuals who cannot tolerate the standard treatment.
- Sulfadiazine (generic name product): sulfonamide antibiotic used with pyrimethamine to treat toxoplasmosis.
- Sulfamethoxazole-Trimethoprim (SMZ-TMP) (generic name product, Bactrim, Cofatrim Forte, Cotrim, Septra, Sulfatrim): the sulfonamide antibiotic, sulfamethoxazole, used in combination with trimethoprim, to prevent and treat PCP and bacterial infections, such as bronchitis and middle ear and urinary tract infections.
- Trimethoprim (generic name product, Proloprim, Trimpex): primarily used to prevent or treat urinary tract infections.
- Vancomycin hydrochloride (generic name product, Vancocin): glycopeptide antibiotic used to treat a variety of serious gram-positive bacterial infections for which other medicines are ineffective, including strains of *Staphylococcus* that are resistant to most oral antibiotics.

Most of these antibiotics kill bacteria by preventing them from making protein for their cell walls. Ciprofloxacin and metronidazole prevent bacteria from reproducing by interfering with their ability to make new DNA. All of these drugs are approved for prescription by the U.S. Food and Drug Administration.

Recommended dosage

Dosages of antibiotics depend on the individual, the infection that is being treated, and the presence of other medical conditions. For children, the dosage usually is based on body weight and is lower than the adult dosage. To be effective, an entire treatment with antibiotics must be completed, even if the symptoms of infection have disappeared. Furthermore, it is important to keep the level of antibiotic in the body at a constant level during treatment. Therefore, the drug should be taken on a regular schedule. If a dose is missed, it should be taken as soon as possible. If it is almost time for the next dose, the missed dose should be skipped. Doubling up doses is generally not recommended.

Average adult dosages of common antibiotics for cancer patients are as follows:

- Atovaquone: for PCP treatment, 750 mg oral suspension twice a day, or tablets three times per day, for 21 days; for PCP prevention, 1,500 mg oral suspension, once a day; must be taken with balanced meals.
- Aztreonam: 1–2 gm every 6–12 hours, injected into a vein, over a 20–60 minute-period.
- Cefepime: 500 mg to 2 gm, injected into a vein or muscle, every 8–12 hours for 7–10 days.
- Ceftazidime: 250 mg to 2 gm, injected into a vein or muscle, every 8–12 hours.
- Ceftriaxone: 1–2 gm, injected into a vein or muscle, every 24 hours.
- Ciprofloxacin: 500–750 mg of the tablet or suspension, every 12 hours, for 3–28 days, taken two hours after meals with 8 oz of water; bone and joint infections usually are treated for at least 4–6 weeks; 200–400 mg injected every 8–12 hours.
- Clindamycin: 150–300 mg of capsule or solution, every six hours; 300–600 mg every six to eight hours or 900 mg every eight hours, injected into a vein or muscle.
- Gentamicin: dosage determined by body weight, every 8–24 hours for at least 7–10 days, injected into a vein or muscle.
- Metronidazole: for bacterial infections, 7.5 mg per kg (3.4 mg per lb) of body weight up to a maximum of 1 gm, every six hours for at least seven days (capsules or tablets); 15 mg per kg (6.8 mg per lb) for the first dose, followed by half that dosage every six hours for at least seven days (injected into a vein); for protozoal infections caused by amebas, 500–750 mg of oral medicine, three times per day for 5–10 days; for trichomoniasis, 2 gm for one day or 250 mg three times per day for seven days (oral medicine); extended-release tablets for vaginal bacterial infections, 750 mg once a day for seven days.
- Pentamidine: for treating PCP, 4 mg per kg (1.8 mg per lb) of body weight, once per day for 14–21 days, injected into a vein over one to two hours, while lying down.

- Pyrimethamine: for toxoplasmosis, 25–200 mg tablets, taken with other medicine, for several weeks.
- Sulfadiazine: for bacterial and protozoal infections, 2–4 gm for the first dose, followed by 1 gm every four to six hours (tablets).
- SMZ-TMP: 800 mg of sulfamethoxazole and 160 mg of trimethoprim, (tablet or oral suspension), every 12 hours for bacterial infections and every 24 hours for prevention of PCP; dosage based on body weight for PCP treatment; injections based on body weight, every six, eight or 12 hours for bacterial infections and every six hours for PCP treatment.
- Trimethoprim: 100 mg tablet every 12 hours for 10 days; for prevention of urinary tract infections, once a day for a long period.
- Vancomycin: 7.5 mg per kg (3.4 mg per lb) of body weight, or 500 mg–1 gram, injected or taken orally, every 6–12 hours.

Precautions

Stomach or intestinal problems or colitis (inflammation of the colon) may affect the use of:

- Atovaquone
- Cephalosporins
- Clindamycin

Kidney or liver disease may affect the use of:

- Aztreonam
- Cefepime
- Ceftazidime
- Ciprofloxacin
- Clindamycin
- Gentamicin
- Metronidazole
- Pentamidine
- Pyrimethamine
- Sulfadiazine
- SMZ-TMP
- Trimethoprim
- Vancomycin

Central nervous system or seizure disorders may affect the use of:

- Ciprofloxacin
- Metronidazole
- Pyrimethamine

Anemia (low red blood cell count) or other blood disorders may affect the use of:

- Metronidazole
- Pentamidine
- Pyrimethamine
- Sulfadiazine
- SMZ-TMP
- Trimethoprim

Ciprofloxacin may not be suitable for individuals with tendinitis or with skin sensitivities to sunlight. Gentamicin may not be suitable for people with hearing problems, **myasthenia gravis**, or Parkinson's disease. Metronidazole may not be suitable for individuals with heart disease, oral or vaginal yeast infections, or a history of alcoholism. Pentamidine may not be suitable for individuals with heart disease, bleeding disorders, or low blood pressure. Pentamidine may affect blood sugar levels, making control of diabetes mellitus or hypoglycemia (low blood sugar) difficult. Vancomycin may not be appropriate for individuals with hearing problems.

Many antibiotics should not be taken during pregnancy or while breast-feeding. Older individuals may be more susceptible to the side effects of sulfadiazine, SMZ-TMP, or trimethoprim.

Side effects

Some individuals may have allergic reactions to antibiotics. If symptoms of an allergic reaction (such as rash, shortness of breath, swelling of the face and neck), severe **diarrhea**, or abdominal cramping occur, the antibiotic should be stopped and the individual should seek medical advice.

Because antibiotics can affect bacteria that are beneficial, as well as those that are harmful, women may become susceptible to infections by fungi when taking antibiotics. Vaginal **itching** or discharge may be symptoms of such infections. All patients may develop oral fungal infections of the mouth, indicated by white plaques in the mouth.

Injected antibiotics may result in irritation, pain, tenderness, or swelling in the vein used for injection. Antibiotics used in cancer patients may have numerous side effects, both minor and severe; however, most side effects are uncommon or rare.

The more common side effects of atovaquone, aztreonam, cephalosporins, ciprofloxacin, clindamycin, gentamicin, metronidazole, and SMZ-TMP include:

- **nausea and vomiting**
- diarrhea
- loss of appetiteEating active cultured yogurt may help counteract diarrhea, but if a patient has low white blood cells, this remedy is not recommended. For mild diarrhea with cephalosporins, only diarrhea medicines containing kaolin or attapulgite should be taken. With clindamycin, diarrhea medicines containing attapulgite should be taken several hours before or after the oral antibiotic. Diarrhea following antibiotics like clindamycin may indicate a bacterial infection that needs additional therapy, and a physician should be consulted.

Other side effects of atovaquone may include:

- **fever**
- skin rash
- cough
- headache
- insomnia

Other side effects of ciprofloxacin may include:

- abdominal pain
- increase in blood tests for kidney function
- dizziness or light-headedness
- inflammation or tearing of a tendon
- drowsiness
- insomnia

Other common side effects of clindamycin include abdominal pain and fever. Side effects may occur up to several weeks after treatment with this medicine.

Gentamicin and vancomycin may cause serious side effects, particularly in elderly individuals and newborn infants. These include kidney damage and damage to the auditory nerve that controls hearing. Other, more common side effects of gentamicin may include:

- changes in urination
- increased thirst
- muscle twitching or seizures
- headache
- lethargy

When gentamicin is injected into a muscle, vein, or the spinal fluid, the following side effects may occur:

- leg cramps
- skin rash
- fever
- seizuresSide effects from gentamicin may develop up to several weeks after the medicine is stopped.

More common side effects of metronidazole include:

- mouth dryness
- unpleasant or metallic taste
- dizziness or light-headedness
- headache
- stomach painSugarless candy or gum, bits of ice, or a saliva substitute may relieve symptoms of dry mouth.

Pentamidine, pyrimethamine, sulfonamides, SMZ-TMP, and trimethoprim can lower the number of white blood cells, resulting in an increased risk of infection. These drugs also can lower the number of blood platelets that are important for blood clotting. Thus, there is an increased risk of bleeding or bruising while taking these drugs.

Serious side effects of pentamidine may include:

- heart problems
- low blood pressure
- high or low blood sugar
- other blood problems
- decrease in urination
- sore throat and fever
- sharp pain in upper abdomenSome of these symptoms may not occur until several months after treatment with pentamidine.

Pyrimethamine and trimethoprim may lower the red blood cell count, causing anemia. **Leucovorin** or the vitamin **folic acid** may be prescribed for anemia.

Some individuals become more sensitive to sunlight when taking sulfonamides, SMZ-TMP, or trimethoprim. Other common side effects of sulfonamides and SMZ-TMP include:

- dizziness
- itching
- skin rash
- headache
- mouth sores or swelling of the tongue
- fatigue

If vancomycin is injected into a vein too quickly, it can cause flushing and a rash over the neck, face, and chest, wheezing or difficulty breathing, and a dangerous decrease in blood pressure.

KEY TERMS

Gram-negative—Types of bacteria that do not retain Gram stain.

Gram-positive—Types of bacteria that retain Gram stain.

Mycobacteria—Rod-shaped bacteria, some of which cause human diseases such as tuberculosis.

***Pneumocystis carinii* pneumonia (PCP)**—Serious type of pneumonia caused by the protozoan *Pneumocystis carinii*.

Protozoa—Single-celled animals.

Toxoplasmosis—Infection caused by the protozoan parasite *Toxoplasma gondii*, affecting animals and humans with suppressed immune systems.

Trichomoniasis—Infection caused by a protozoan of the genus *Trichomonas*; especially vaginitis caused by *Trichomonas vaginalis*

Interactions

Many prescription and non-prescription medicines can interact with these antibiotics. Therefore, it is important to consult a complete list of known drug interactions. Among the more common or dangerous interactions:

- Antibiotics that lower the number of blood platelets, with blood thinners (anticoagulants), such as warfarin
- Aztreonam and metronidazole with alcohol; it is important not to consume alcohol until at least three days after treatment with these antibiotics
- Ciprofloxacin with antacids, iron supplements, or caffeine
- Pentamidine or pyrimethamine with previous treatments with x rays or cancer medicines (increased risk of blood cell damage)
- Trimethoprim with diuretics to remove excess fluid in the elderly

Many medicines can increase the risk of hearing or kidney damage from gentamicin. These include:

- cisplatin
- combination pain medicine with acetaminophen and aspirin or other salicylates (taken regularly in large amounts)
- **cyclosporine**
- inflammation or pain medicine, except narcotics
- lithium
- methotrexate
- other medicines for infection

The following drugs may increase the risk of liver effects with sulfadiazine or SMZ-TMP:

- acetaminophen, long-term, high-dose (eg Tylenol)
- birth control pills containing estrogens
- disulfiram (Antabuse)
- other medicines for infection

Resources

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Margaret Alic, Ph.D.

Antidiarrheal agents

Definition

Antidiarrheal agents are prescription and non-prescription medicines that are used to treat **diarrhea**.

Purpose

Some types of cancer may cause diarrhea. In addition, diarrhea is a common side effect of **chemotherapy** treatments for cancer. This is because anticancer drugs can damage the cells of the intestines. Radiation treatment for cancer directed at the abdominal region also may cause diarrhea. Diarrhea can result in dehydration and the loss of minerals such as potassium. It may prevent the elimination of waste products in the urine, as the body attempts to conserve water.

Description

The common medicines for treating diarrhea that results from cancer and cancer treatments are:

- atropine and diphenoxylate
- loperamide
- octreotide
- opium tincture

Atropine and diphenoxylate are prescribed as a combination medicine with the brand names:

- Lofene
- Logen
- Lomocot
- Lomotil
- Lonox
- Vi-AtroThe generic name product also may be available. Atropine and diphenoxylate, antiperistaltic and anticholinergic agents, relax muscles and slow down the movements of the gastrointestinal tract. Diphenoxylate is similar to some narcotics and may be habit-forming if taken in dosages higher than prescribed. Since higher doses of atropine have unpleasant effects, it is unlikely that the combination medicine will be taken in high enough doses to cause diphenoxylate-dependence.

Loperamide slows down the movements of the intestines. The common brand names for this medicine are:

- Imodium
- Kaopectate II
- Maalox Anti-Diarrheal
- Pepto Diarrhea Control

Octreotide (brand name Sandostatin) is used to treat diarrhea and other symptoms of some types of intestinal cancers. It also is used to treat insulin-producing tumors of the pancreas and diarrhea caused by chemotherapy.

Opium tincture, also known as camphorated opium tincture or laudanum, is a narcotic that is used to treat severe diarrhea.

Except for loperamide liquid or tablets, all of these medicines require a prescription. Dosages vary with the individual.

Recommended dosage

The atropine-diphenoxylate combination is taken by mouth as a solution or a tablet. It may be taken with food to reduce stomach upset. The initial average dosage is 5 mg (2 tsp or two tablets) three to four times daily. Subsequent doses are once daily, as needed.

Loperamide is taken orally, as a liquid, tablet, or capsule. The usual dosage for adults and teenagers is 4 mg (2 capsules or tablets, 4 tsp of liquid) after the first loose bowel movement, followed by 2 mg after each successive loose bowel movement. The maximum dose is 16 mg of the capsules or 8 mg of the tablets or liquid in 24 hours. Loperamide should not be taken for more than two days unless ordered by a physician.

Following therapy with **irinotecan** (Camptosar), loperamide doses of 2 mg every two hours while awake and 4 mg every four hours at night are utilized at the onset of diarrhea to prevent severe dehydration and possible hospitalization.

Octreotide is packaged as a kit, for injection into a vein. For treating severe diarrhea from intestinal tumors, the average initial dosage of the long-acting form, for adults and teenagers, is 20 mg injected into the gluteal muscle of the buttocks, once every four weeks for two months. The dosage may then be adjusted by the physician. For the short-acting form, the average initial dose is 50 micrograms (mcg) injected under the skin, two to three times per day. The dosage may be gradually increased up to 600 mcg per day for the first two weeks. The average dosage after two weeks is 50–1500 mcg per day. For children, the usual dosage is 1–10 mcg per kg (0.45–4.5 mcg per lb) of body weight per day.

Opium tincture is taken orally, as a liquid. It may be taken with food to prevent stomach upset. The average adult dose is 5–16 drops, measured from the dropper in the bottle, four times per day, until diarrhea is controlled. It may be diluted with water. After several weeks of treatment, it may be necessary to lower the dosage gradually before stopping the medicine, to lessen the risk of side effects from opium withdrawal.

Precautions

Antidiarrheal agents may cause allergic reactions in some individuals. Atropine and diphenoxylate should not be given to children. Loperamide should not be given to children under six. Opium may cause breathing problems in children up to two years of age. Older adults are more sensitive to diphenoxylate and opium than younger individuals and these drugs may cause breathing problems. Diphenoxylate and loperamide may mask the symptoms of dehydration caused by diarrhea in older individuals, so it is very important to drink sufficient fluids.

Atropine and diphenoxylate

Other medical conditions may affect the use of atropine and diphenoxylate:

- alcohol or drug abuse may increase the risk of diphenoxylate addiction
- colitis (inflammation of the colon) may become more severe
- Down syndrome may cause more severe side effects
- dysentery may worsen
- emphysema, asthma, bronchitis, or other chronic lung diseases increase the risk of breathing problems
- enlarged prostate or urinary tract blockage may cause severe problems with urination
- gall bladder disease or gallstones may worsen
- glaucoma may result in severe eye pain (rare)
- heart disease may worsen
- hiatal hernia may worsen with atropine (rare)
- high blood pressure may increase (rare)
- intestinal blockage may worsen
- kidney disease may cause atropine to accumulate in the body, resulting in side effects
- liver disease may cause central nervous system side effects, including coma
- myasthenia gravis may become worse
- overactive or underactive thyroid may cause effects on breathing and heart rate
- incontinence may worsen

An overdose of atropine and diphenoxylate can lead to unconsciousness and death. Symptoms of overdose include:

- severe drowsiness
- breathing problems
- fast heartbeat
- warmth, dryness, and flushing of skin
- vision problems
- severe dryness of mouth, nose, and throat
- nervousness or irritability

Loperamide and octreotide

Other medical conditions may affect the use of loperamide:

- colitis (inflammation of the colon) may worsen
- dysentery may worsen
- liver disease may increase the risk of side effectsLoperamide should not be used in the presence of **fever** or blood or mucus in stools.

Medical conditions that may affect the use of octreotide include:

- diabetes mellitus, since octreotide may affect blood sugar levels
- gallbladder disease or gallstones, since octreotide may cause gallstones
- severe kidney disease that may cause octreotide to remain in the body longer

Opium tincture

Side effects of opium tincture may be increased or become dangerous when combined with the following medical conditions:

- alcohol or drug abuse
- colitis (inflammation of the colon)
- heart disease
- kidney disease
- liver disease
- underactive thyroid
- head injury or brain disease
- emphysema, asthma, bronchitis, or other chronic lung disease
- problems with urination or enlarged prostate
- gallbladder disease or gallstones
- seizures

Opium tincture may be habit-forming, causing mental or physical dependence that can lead to side effects of withdrawal when stopping the medicine. The use of opium tincture during pregnancy can cause dependency in the fetus and symptoms of drug withdrawal or breathing problems in the newborn infant.

Symptoms of opium overdose include:

- seizures
- confusion
- severe restlessness or nervousness
- severe dizziness
- severe drowsiness
- slow or irregular breathing
- severe weakness
- cold, clammy skin
- low blood pressure

- slow heartbeat
- contracted eye pupils

Side effects

Atropine and diphenoxylate

At low doses, taken for short periods of time, side effects of atropine and diphenoxylate are rare. However, serious side effects may include:

- bloating
- constipation
- loss of appetite
- stomach pain with nausea and vomiting

Other, less common or rare side effects of atropine and diphenoxylate include:

- dizziness
- drowsiness
- blurred vision
- confusion
- difficult urination
- dry skin or mouth
- fever
- headache
- depression
- numbness in hands or feet
- skin rash or itching
- swelling of gums

Rare side effects that may occur after stopping atropine and diphenoxylate include:

- sweating
- trembling or chills
- muscle cramps
- nausea or vomiting
- stomach cramps

Loperamide

Side effects are rare with low dosages of loperamide, taken for a short time. However, severe side effects may include:

- bloating
- constipation
- loss of appetite
- stomach pain with nausea and vomiting
- skin rash
- dry mouth
- dizziness or drowsiness

Octreotide

More common side effects of octreotide may include:

- irregular or slow heartbeat
- constipation
- diarrhea
- flatulence
- discomfort at the site of injection

Less common or rare side effects of octreotide may include:

- dizziness or light-headedness
- fever
- flushing or redness of the face
- swelling of feet or lower legs
- inflammation of the pancreas with stomach pain, nausea, or vomiting
- hair loss
- seizures
- unconsciousness

Symptoms of high blood sugar (hyperglycemia) from octreotide include:

- blurred vision
- drowsiness and **fatigue**
- dry mouth
- flushed, dry skin
- fruity breath odor
- increased urination
- ketones in urine
- loss of appetite
- increased thirst
- nausea or vomiting
- stomach ache
- rapid, deep breathing

Symptoms of low blood sugar (hypoglycemia) from octreotide include:

- anxiety and nervousness
- confusion

- blurred vision
- cold sweats
- cool, pale skin
- drowsiness, fatigue, weakness
- hunger
- fast heartbeat
- headache
- nausea
- nightmares and restless sleep
- shakiness
- slurred speech

Opium tincture

Side effects of opium tincture that are more common with higher dosages may include:

- drowsiness
- dizziness, light-headedness, faintness
- nervousness
- weakness or fatigue
- painful or strained urination
- frequent urination
- decreased volume of urineLying down and rising slowly from a seated or lying position may help relieve dizziness.

Rare side effects of opium tincture include:

- bloating
- constipation
- loss of appetite
- nausea or vomiting
- stomach cramps
- fast or slow heartbeat
- sweating
- rash, hives, or itching
- redness or flushing of the face
- depression
- troubled breathing
- convulsions (seizures)

The following side effects may occur after stopping treatment with opium tincture:

- runny nose or sneezing
- body aches
- loss of appetite
- diarrhea
- stomach cramps
- nausea or vomiting
- fever
- sweating
- nervousness or irritability
- trembling
- insomnia
- dilated pupils
- severe weakness

Interactions

Atropine and diphenoxylate

Other drugs may interact with atropine and diphenoxylate:

- **Antibiotics** (cephalosporins, clindamycin, erythromycins, tetracyclines) can counteract the effects of atropine and diphenoxylate and make the diarrhea worse.
- Central nervous system depressants (alcohol, antihistamines, sedatives, pain medicines or narcotics, barbiturates, seizure medicine, muscle relaxants, anesthetics) may increase effects, such as drowsiness, from both the depressant and the antidiarrheal agent.
- Monoamine oxidase inhibitors may cause severe side effects if taken within two weeks of diphenoxylate and atropine.
- Opioid antagonists (naltrexone) may cause withdrawal from diphenoxylate addiction; naltrexone will counteract the antidiarrheal effects of the medicine.
- Other anticholinergics to reduce stomach acid or cramps may increase the effects of atropine.

Loperamide and octreotide

Antibiotics may interact with loperamide and make the diarrhea worse. Narcotic pain medicines in combination with loperamide may cause severe constipation.

Because octreotide may cause high or low blood sugar, it can interact with the following medicines:

- antidiabetic medicines, sulfonylurea
- diazoxide (Proglycem)
- glucagon
- insulin
- growth hormone

KEY TERMS

Anticholinergic agent—Drug that slows the action of the bowel by relaxing the muscles; reduces stomach acid.

Antiperistaltic agent—Drug that slows the contraction and relaxation (peristalsis) of the intestines.

Opium tincture

The following medicines may increase side effects from opium tincture:

- anticholinergics for abdominal or stomach cramps
- other antidiarrheal medicines
- tricyclic antidepressants Naltrexone (Trexan) makes opium less effective for treating diarrhea. Alcohol, narcotics, and other central nervous system depressants, including antihistamines, sedatives, prescription pain medicines, barbiturates, seizure medicines, muscle relaxants, or anesthetics, may lead to unconsciousness or death in combination with opium tincture.

Margaret Alic, Ph.D.

Antiemetics

Definition

Antiemetic drugs are drugs used to combat **nausea and vomiting**.

Purpose

Antiemetic drugs are used to prevent vomiting (emesis) in **chemotherapy** patients and postoperative patients. Aside from the difficulty of maintaining proper nutrition and a healthy weight, chronic vomiting can result in dehydration, which can be a medical emergency. Following are descriptions of many common antiemetic drugs in use as of 2004.

Description

Promethazine

Promethazine is also known as phenergan and mepergan. It is also used to treat motion sickness, reduce allergic symptoms, and for sedation. It is one of the drugs of the phenothiazine type. In addition to other qualities, it is an antihistamine.

Prochlorperazine

Prochlorperazine is also known as compazine. Like promethazine, it is a member of the class of phenothiazines. Unlike promethazine, however, prochlorperazine also belongs to the class of drugs known as antipsychotics, or neuroleptics. Antipsychotic drugs are used to treat psychoses and other psychiatric disorders. In addition to its use as an antiemetic and anti-psychotic drug, prochlorperazine is also used to treat non-psychotic anxiety.

Serotonin receptor antagonists

The serotonin receptor antagonists include granisetron (kytril), dolasetron (anzemet), and ondansetron (zofran). These drugs are used for postoperative nausea and emesis as well as nausea and vomiting associated with chemotherapy, and are often used in combination with a corticosteroid. Ondansetron is approved for nausea and vomiting associated with **radiation therapy**.

Neurokinin receptor antagonists

The Neurokinin receptor antagonists are a new class of antiemetics. Aprepitant (Emend) was approved in 2004 for use in cancer patients. It is used in combination with other antiemetics for relief of acute and delayed nausea and vomiting caused by high-dose chemotherapy, most often caused by the chemotherapy drug cisplatin.

Dronabinol

Dronabinol (marinol) is used to combat **anorexia** in AIDS patients, and emesis in cancer patients who haven't responded to other antiemetics. Marinol is the synthetic or extracted form of the active ingredient found in **marijuana**.

Other antipsychotic (neuroleptic) drugs

The other neuroleptic (antipsychotic) drugs used to treat nausea and emesis are droperidol (inapsine), haloperidol (haldol), chlorpromazine (thorazine), and perphenazine (trilafon). One other antipsychotic, triethylperazine (torecan or norzine), was used as an antiemetic, but is no longer widely available. Some of the antipsychotics are also used to treat aggressive or violent behavior or incontrollable hiccups (chlorpromazine). These drugs are similar to prochlorperazine in terms of their actions and potentially severe side effects.

Dosage

Promethazine

Promethazine is given in doses of 12.5 to 25 mg every 4 hours if injected into the muscle or as a supposi-

tory. As a syrup, 25 mg should be given every 4 to 6 hours. Doses for children vary by age, weight, and severity of condition.

Prochlorperazine

Generally, the dose is 5 to 10 mg, 3 to 4 times per day. However, the effect of medication varies widely from patient to patient, so the dose should be tailored to each individual. Prochlorperazine is available as a syrup, tablet, 25 mg slow-release capsule, and in injectable form.

Aprepitant

One 125-mg capsule is given by mouth one hour before chemotherapy begins. An 80-mg capsule is taken each morning for two days following the chemotherapy treatment.

Dronabinol

The effective dose of dronabinol varies widely from patient to patient and should be monitored and tested by the physician. The basic dose is $5mg/m^2$ given 4 to 6 times per day.

Precautions

Promethazine

Patients with cardiovascular disease or impaired liver function should either use this drug with caution or not at all. Children should also use this drug cautiously for two reasons. First, some side effects may suggest, or mask, underlying disease, such as Reye's syndrome. Second, large doses of this drug, or any antihistamine, may cause convulsions, hallucinations, or death in children. Patients taking this medication should not drive, operate heavy machinery, or engage in any hazardous activity while under the influence of this drug. This drug has not been established as safe for use during pregnancy, or in nursing mothers.

Prochlorperazine

Persons allergic to any other phenothiazine (such as promethazine) should not take prochlorperazine. Patients who have heart problems, glaucoma, or bone marrow depression should take this drug with caution, or not at all, and inform their physician of their condition. People who will be around high temperatures should also avoid this drug. In addition, those who experience seizures should be aware that administration of this drug makes seizures more likely.

Breast cancer patients may wish to avoid this drug because it increases levels of prolactin in the blood. Increased prolactin may help some types of breast cancer to thrive.

Prochloroperazine, like promethazine, may mask symptoms of Reye's disease in children. It may also mask symptoms of intestinal obstructions or brain disease. In addition, children who are acutely ill, under two years of age, or under 20 pounds should not be given this drug.

This drug has not been established as safe for use during pregnancy and is found in the breast milk of lactating mothers. Therefore, caution should be used when administering this drug to pregnant women and extreme caution should be used when administering to nursing women.

Aprepitant

Patients should not drink grapefruit juice while taking aprepitant. The physician should be told if the patient is pregnant, breast feeding, or becomes pregnant while taking the drug.

Serotonin receptor antagonists

Patients with allergies to any drug in this category should not take any other drug in this category. Also, patients with hypokalemia, hypomagnesia, or certain heart problems should avoid taking these drugs. The effect of these drugs on the children or fetuses of nursing or pregnant mothers is not known, so they should be used with caution.

Dronabinol

Dronabinol is inadvisable for patients with a known allergy to either sesame oil or any part of the cannabis plant. Patients taking this drug should not drive, operate heavy machinery, or engage in hazardous tasks until used to this medication.

This medication also should be used cautiously, if at all, for persons with depression, mania, or schizophrenia, elderly patients, patients with cardiac disorders, and for pregnant and nursing women. It is especially inadvisable for nursing women, since marinol is concentrated in the breast milk.

Side effects

Promethazine

Patients taking promethazine may experience a large number of side effects, including drowsiness, ringing in the ears, a lack of coordination, problems with vision, **fatigue**, euphoria, nervousness, tremors, seizures, a catatonic-like state, and hysteria. These effects are usually reversible. At high doses, patients may also exhibit

extrapyramidal reactions. Extrapyramidal reactions can briefly be described as agitation (jitteriness, sometimes insomnia), muscle spasms, and/or pseudo-Parkinson's (a group of symptoms including, but not limited to, drooling, tremors, and a shuffling gait).

Patients may also experience rashes, asthma, jaundice, abnormally low production of white blood cells, and abnormalities in how fast or slow their heart beats. Patients may sometimes experience unusual side effects not known as typical for the medication they are taking. These should be reported to the physician.

Prochlorperazine

Prochlorperazine has many side effects, including low blood pressure, dizziness, blurred vision, skin reactions, and jaundice. Patients also may suffer jaw, neck, and back muscle spasms, slow or difficult speech, and difficulty swallowing, as well as rhythmic face, mouth, or jaw movements. However, the most severe side effects stem from damage to the brain after long-term use. These symptoms may be reversed by treating the patient with drugs effective in treatment of Parkinson's patients (except levodopa). A reduction or elimination in the amount of the antipsychotic medication may also be necessary to eliminate these symptoms.

Two other (rare) disorders, tardive dyskinesia and neuroleptic malignant syndrome (NMS), are also associated with antipsychotic drug use. Patients with NMS have high temperatures, rigid muscles, an altered mental state, and symptoms such as excessive sweating and irregular blood pressure or heart rhythm. Patients with NMS usually respond to treatment. Patients with tardive dyskinesia have involuntary movement of muscles in the chest, arms, and legs, or in the muscles in and around the face (including the tongue). Tardive dyskinesia may be irreversible.

Aprepitant

Side effects of aprepitant include fatigue, dizziness, stomach pain, nausea, hiccups, diarrhea, constipation, and loss of appetite. More serious, but less common, side effects have been reported, including hives, skin rash, difficulty breathing or swallowing, hoarseness, and swelling in the face, throat, tongue, lips, eyes, feet, ankles, or lower legs. If any of these more serious side effects occur, the patient should contact the treating physician immediately.

Serotonin receptor antagonists

Side effects include rashes, increased sweating, problems with taste or vision, flushing, agitation, sleep disorder, depersonalization, headache, fatigue, nausea, weakness, abdominal pain, constipation, **diarrhea**, hypertension, dizziness, chills and shivering, and dry mouth. Patients may also have abnormal liver function tests.

Dronabinol

Possible side effects are fatigue, weakness, abdominal pain, nausea, vomiting, heart palpitations, fast heart rate, facial flushing, amnesia, anxiety, an abnormal mental state, depersonalization, confusion, dizziness, and euphoria.

There are certain additional precautions and side effects associated with each of these drugs. Patients should be sure to notify their physician of any health concerns (including pregnancy) or medications they are taking. Patients should also ask about potential side effects for each individual medication before receiving any of these drugs.

Interactions

Promethazine

Promethazine interacts with central nervous system depressants, like alcohol and barbiturates. Therefore, the physician should be alerted to any medications the patient is taking, and doses of the drugs should be adjusted accordingly. Alcohol should be avoided. It has not been proven, but promethazine may interfere with the action of epinephrine.

Prochlorperazine

Like promethazine, prochlorperazine should be used cautiously, or not at all, with central nervous system depressants like alcohol and barbiturates. Prochlorperazine has also been shown to interact with anticonvulsant medication, guanethidene, propanolol, thiazide diuretics, and oral anticoagulants (like **warfarin** and coumadin).

Aprepitant

A physician can check the long list of possible drug interactions, which include possible effects on the action of certain chemotherapy drugs. Aprepitant also may interact with the blood thinner warfarin (Coumadin) and other popular drugs. The treating physician or pharmacist will need a complete list of other drugs the patient is taking before prescribing this antiemetic.

Serotonin receptor antagonists

These drugs may have very negative effects on the patient when combined with diuretics, anti-arrhythmia drugs, or high doses of anthracycline.

KEY TERMS

Depersonalization—An alteration in the perception of self.

Tardive dyskinesia—A disorder brought on by antipsychotic medication use, characterized by uncontrollable muscle spasms.

Dronabinol

Dronabinol interacts with the antiemetic prochlorperazine synergistically. Therefore, the use of these two drugs in combination results in a greater antiemetic effect. Patients taking central nervous system depressants, such as barbiturates or alcohol should notify their physician before taking marinol, since marinol may increase their effect. Although no drugs have been shown to interact with marinol, many drugs similar to marinol do interact with a number of other drugs, including central nervous system depressants such as alcohol or barbiturates, or drugs like flouxetine or disulfiram. Again, the physician should be alerted to any medications the patient is taking before beginning a course of dronabinol.

See also Corticosteroids; Lorazepam; Metoclopramide.

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Antiestrogens

Definition

Antiestrogens are a group of medications that block the effect that estrogen has on the growth of a tumor.

Purpose

For about 20 years, antiestrogens have been used mainly to help prevent and treat breast cancer. Since many breast cancer tumors use hormones to fuel their growth, blocking the hormones limits their ability to grow.

Description

Antiestrogens refer to a group of drugs. Many **breast cancer** tumors grow due to normal levels of estrogen, a hormone found in the bloodstream. Some patients have tumors that are extra-sensitive to this normal estrogen level. The estrogen attaches to the area on the outside of the tumor cells and sends a signal to the cell that causes it to grow and multiply. Antiestrogens block the protein on the outside wall of the estrogen-sensitive breast cancer cell. By blocking this protein, known as the estrogen receptor, the free-floating estrogen cannot stimulate the cancer cells to grow and multiply any further.

The drug **tamoxifen** is a common antiestrogen that has proven to have a positive effect in breast cancer patients for both treatment and prevention.

The drug **raloxifene** is a newer antiestrogen. Early research showed that raloxifene worked against breast cancer with fewer side effects than tamoxifene. In 2003, research also showed that raloxifene may be effective in decreasing new fractures among women with low bone mineral density. However, further clinical trials on raloxifene are needed.

Precautions

Use of tamoxifen has been associated with a number of side effects, including vaginal bleeding, menstrual irregularities, and hypercalcemia (excess calcium in the blood). Most women also experience hot flashes while using the drug. Serious side effects include endometrial cancer and thromboembolism (blocking of a blood vessel by a particle of a blood clot at the site the blood clot formed). In late 2003, cancer experts were beginning to recommend a new group of drugs called aromatase inhibitors (Arimidex, common name anastrozole or Femara and Novartis, common name letrozole) as an alternative to tamoxifen or following tamoxifen therapy. These drugs fight breast cancer differently, but early research shows they fight it as effectively and with fewer side effects.

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Antifungal therapy

Definition

Antifungal drugs are used to treat infections caused by fungi and to prevent the development of fungal infections in patients with weakened immune systems.

Purpose

Fungal infections

A fungus is a living organism that can cause infection when it grows in the human body. In healthy people, fungal infections tend to be mild and treatable. For cancer patients, however, fungal infections can become severe and must be treated quickly. Cancer patients, particularly those with leukemia or **lymphoma**, tend to have weakened immune systems as a result of **chemotherapy** or the disease. Once they are infected, their weak immune system allows the fungus to grow quickly. Because of this risk, some cancer patients with no obvious fungal infection are given antifungal therapy to help prevent infection from developing. This approach to treatment is called prophylaxis or prophylactic therapy.

Fungal infection can occur in two ways. Some fungi, such as candida, are usually found in the bodies of healthy people and cause little or no harm. When the immune system is weak, however, these fungi begin to grow and cause infection. Other fungi, such as aspergillus and cryptococcus, are found in the air. Infection occurs when the fungus is either inhaled into the lungs or comes into contact with an operative wound. The most common fungal infections found in patients with weakened immune systems are candidiasis, aspergillosis and cryptococcosis.

Diagnostic innovations in antifungal therapy in cancer patients include the increased use of nonculture-based tests to speed up the process of diagnosis.

Treatment

The treatment of a fungal infection depends on the type and location of infection. Superficial infections that affect the skin, hair, and nails can be treated with topical (cream or ointment) or oral antifungal drugs. Systemic infections that affect the internal organs require aggressive treatment with either oral or intravenous drugs.

Description

There are three classes of drugs typically used to treat fungal infections: polyenes, azoles, and echinocandins.

Polyenes

Polyenes are drugs that work by attaching to the sterol component found in the fungal membrane, causing the cells to become porous and die. The two polyenes most commonly used are nystatin (Mycostatin) and amphotericin B (Fungizone). Nystatin is often used as a topical agent to treat superficial infections, or is taken orally to treat such candidal infections as oral or esophageal candidiasis.

Amphotericin B was the first antifungal drug to be approved for use, and it is still the standard therapy for the most severe systemic fungal infections. Recently, several new types of amphotericin B (Abelcet, Amphotec and AmBisome) have been introduced. These drugs, called lipid formulations, cause fewer side effects than traditional amphotericin B but are more expensive.

Azoles

Azoles stop fungal growth by preventing fungi from making an essential part of their cell wall. Three typical azoles are ketoconazole (Nizoral), fluconazole (Diflucan), and itraconazole (Sporanox). Ketoconazole is the oldest of these three drugs, and has been used since the 1970s. It is slightly more toxic than the other azoles and does not work for aspergillosis and many candidiasis infections.

Although fluconazole is effective against both superficial and systemic candidiasis, some strains of this fungus have now become resistant to the drug. Itraconazole, the newest of the azoles, is effective against a range of different fungal infections. Unlike ketoconazole or fluconazole, it can be used to treat aspergillosis.

Newer azole medications include voriconazole (Vfend), approved by the FDA in the fall of 2001, and posaconazole, still in clinical trials as of 2004.

Echinocandins

Echinocandins are a new class of antifungal drugs that work by disrupting the wall that surrounds fungal cells. Caspofungin (Cancidas) is the first of this new class of drugs to be approved. It is an effective treatment for severe systemic fungal infections, and is given to

patients who do not respond to other therapies. Micafungin, another drug in this class, has been used in Japan to treat aspergillosis in leukemia patients but has not been approved by the FDA for use in the United States.

Recommended dosage

Although dosages differ for the various antifungal treatments, most therapies continue even after there is no sign of infection.

Polyenes

Topical nystatin should be liberally applied two to three times daily. Liquid formulations of the drug are usually taken in doses of 400,000 to 600,000 units four times a day for adults and children. The dose for the oral tablets is 500,000 to 1 million units every 8 hours. Both traditional amphotericin B and the new lipid formulations of the drug are given intravenously. Dosages are adjusted according to each patient's tolerance and the severity and location of the infection. Patients receiving amphotericin B treatment are usually hospitalized.

Azoles

Ketoconazole is available as a tablet and as a topical treatment. Both treatments are usually given once daily. Treatment can last for several weeks for superficial infections, or up to a year for more serious infections. Fluconazole and itraconazole are both administered either orally or intravenously. The dose depends on the type of fungal infection, the patient's condition and the response to treatment.

Echinocandins

Caspofungin is given intravenously once daily, and most patients receive the same dose.

Precautions

Patients who are given topical or oral antifungal therapy should make sure they use their medication regularly, and for as long as their doctor thinks is necessary. Infections that are not completely eradicated frequently recur.

Side effects

Antifungal drugs that are applied topically rarely cause side effects unless the patient is allergic to the drug. Side effects are more common when drugs are taken orally or intravenously. The most common reactions from azole drugs are nausea, **diarrhea** and other gastrointestinal symptoms. These symptoms usually affect less than 10% of patients. Caspofungin also produces few side effects. The most common side effect is a rash.

KEY TERMS

Aspergillosis—A fungal infection that can be life-threatening to patients with a weakened immune system.

Candidiasis—A fungal infection that can be mild or very serious depending on what part of the body it infects.

Cryptococcosis—A fungal infection that can cause meningitis.

Intravenous—A treatment that is given directly into the bloodstream.

Prophylactic—Referring to a drug or other treatment given to prevent disease.

Topical—A treatment that is applied directly to the skin.

Amphotericin B can be quite toxic and most patients experience side effects. These include **fever**, rigors, and chills. Premedication with acetaminophen, **diphenhydramine**, hydrocortisone, and sometimes meperidine can be given to prevent these side effects. Amphotericin B can also seriously damage the kidneys. However, patients are carefully monitored while taking this drug. If symptoms develop, the liposomal alternative is usually given. Lipid formulations of amphotericin B are far less damaging to the kidneys.

Interactions

Drug interactions are significant with antifungal treatment. Patients taking amphotericin B should not take any other drug that can cause kidney damage. Potentially serious reactions can occur when patients taking azole antifungal therapies also take certain antihistamines such as astemizole (Hismanal) or the statin drug lovastatin (Mevacor). Patients on antifungal therapy who plan to take other prescribed, over the counter, or alternative medicines should always check with their doctor first.

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United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

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Antimicrobials

Definition

Antimicrobial drugs are used to fight infections caused by bacteria, fungi, and viruses.

Description

Antimicrobial drugs are drugs designed to kill, or prevent the growth of microorganisms (bacteria, fungi, and viruses). Bacteria, fungi, and viruses are responsible for almost all of the common infectious diseases found in North America from athlete's foot, to AIDS, to ulcers (as of 2001). Interestingly enough, many disorders formerly thought to be caused by other factors, like stress, are now known to be caused by bacteria. For example, it has been shown that many ulcers are caused by the bacteria *Helicobacter pylori*, and not by stress, as many originally thought. Thus, antimicrobials represent an important part of medicine today.

The history of antimicrobials begins with the observations of Pasteur and Joubert, who discovered that one type of bacteria could prevent the growth of another. They did not know at that time that the reason one bacteria failed to grow was that the other bacteria was producing an antibiotic. Technically, **antibiotics** are only those substances that are produced by one microorganism that kill, or prevent the growth, of another microorganism. Of course, in today's common usage, the term antibiotic is used to refer to almost any drug that cures a bacterial infection. Antimicrobials include not just antibiotics, but synthetically formed compounds as well.

The discovery of antimicrobials like penicillin and tetracycline paved the way for better health for millions around the world. Before 1941, the year penicillin was discovered, no true cure for gonorrhea, strep throat, or **pneumonia** existed. Patients with infected wounds often had to have a wounded limb removed, or face death from infection. Now, most of these infections can be easily cured with a short course of antimicrobials.

However, the future effectiveness of antimicrobial therapy is somewhat in doubt. Microorganisms, especially bacteria, are becoming resistant to more and more antimicrobial agents. Bacteria found in hospitals appear to be especially resilient, and are causing increasing difficulty for the sickest patients–those in the hospital. Currently, bacterial resistance is combated by the discovery of new drugs. However, microorganisms are becoming resistant more quickly than new drugs are being found, Thus, future research in antimicrobial therapy may focus on finding how to overcome resistance to antimicrobials, or how to treat infections with alternative means.

Michael Zuck, PhD

Antineoplastic agents

Definition

Antineoplastic agents are a group of specialized drugs used primarily to treat cancer (the term "neoplastic" refers to cancer cells).

Description

The first antineoplastic agents, used in the 1940s, were made from either synthetic chemicals or natural plants. Antineoplastic agents are classified by origin and by how they work to destroy cancer cells. There are over fifty of these agents approved by the Food and Drug Administration (FDA) to be used in the United States. These include: **methotrexate**, 5-fluorouracil (**fluorouracil**), **doxorubicin**, **paclitaxel**, and **cyclophosphamide**.

Antineoplastic agents can be administered to patients alone or in combination with other antineoplastic drugs. They can also be given before, during or after a patient receives surgery or **radiation therapy**. The treatment plan is disease-specific. It is important that patients receive treatment on schedule.

Antineoplastic agents travel the body and destroy cancer cells. Side effects are expected to occur when treated with these agents, and can include nausea, mouth sores, hair loss, and lowering of the blood counts. Many of the side effects associated with antineoplastic agents occur because **chemotherapy** treatment destroys the body's normal cells in addition to cancerous cells. Healthcare providers should be able to assist patients in managing these side effects so that antineoplastic therapy is a tolerable treatment.

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Antioxidants

Definition

Antioxidants are chemical compounds that can bind to free oxygen radicals preventing these radicals from damaging healthy cells.

Purpose

Preliminary studies have suggested that antioxidants are useful in a number of ways in regards to cancer. For instance, they may improve the effectiveness of **chemotherapy**, decrease side effects of chemotherapy and radiotherapy, and prevent some types of cancer. Sufficient epidemiological studies have shown that ingesting foods high in antioxidants, such as fruits and vegetables, can decrease the risk of many types of cancer. Studies also found that cancer patients have lower levels of antioxidants in their blood.

In early 2004, the National Cancer Institute (NCI) released a new fact sheet concerning cancer prevention and antioxidants. Fruits and vegetables are high in antioxidants and evidence continued to support the role of vitamins C, E, and A, as well as lycopene and beta-carotene in helping to prevent cancer. However, clinical trial results have not been consistent. The NCI reported that three large clinical trials were trying to better answer the role of antioxidants in cancer prevention.

Precautions

Studies of antioxidant supplements to decrease the risk of cancer have not been conclusive. Most antioxidant research has centered around **vitamins** A (and its provitamin, beta-carotene), C, E (alpha-tocopherol), and the trace element selenium. While some studies have shown positive effects for antioxidants in preventing cancer, they have been conducted mostly in underfed populations or persons otherwise deficient in these antioxidants. The CARET studies in the early 1990s found that if smokers take beta-carotene and vitamin A supplements they actually increase their risk of developing lung cancer. Rather than isolated antioxidants found in supplements, it may be the combination of antioxidants found in foods that are responsible for decreasing the risk of cancer. The American Institute of Cancer Research warns that antioxidant supplements cannot substitute for whole foods. Individuals who may want to consider supplements include those who are underfed, have certain medical conditions, chronic dieters, some vegetarians, some seniors, and newborns.

Concern has developed about potential negative interactions between high doses of antioxidants and chemotherapy. Anthracycline antitumor **antibiotics** used as chemotherapy act by creating free oxygen radicals to kill tumor cells through a process known as apoptosis. Although patients taking antioxidants may improve their tolerance to chemotherapy drugs, they may be decreasing the effectiveness of treatment and risking a recurrence of the tumor in the long run. This viewpoint is theoretical, however, and no clinical studies have as yet addressed it. Patients interested in using antioxidants during chemotherapy or radiotherapy should discuss this option with their physicians.

High doses of vitamins and minerals can be toxic. The National Academy of Sciences has suggested safe upper intake levels for adults for some antioxidants. These limits are 2,000 milligrams of vitamin C per day from both foods and supplements combined, 1,000 milligrams of vitamin E per day, and 400 micrograms per day of selenium from both supplements and foods. It is not

KEY TERMS

Apoptosis—A type of cell death. A mechanism by which one cell dies if it becomes severely mutated as a means of protecting the entire organism.

Cisplatin—An anticancer drug.

Doxorubicin—An anticancer antibiotic therapy. Its trade name is Adriamycin

Fluorouracil—An anticancer drug. Its trade names include Adrucil, 5-FU, Efudex, and Fluoroplex.

Mutation—A change in the genetic structure of the cell.

Oxidative stress—A condition where the body is producing an excess of oxygen-free radicals.

known how higher levels than these will affect healthy persons.

Side effects of vitamin E overdose may include **fatigue**, intestinal cramping, breast soreness, thrombophlebitis, acne, and **diarrhea**, and increase in blood pressure in certain people. Blood clotting time has been shown to increase. Vitamin E is antagonistic to iron at certain levels. Patients with **anemia** who are taking iron supplements should not take the two supplements at the same time. Vitamin E also may interfere with vitamin K. Selenium toxicity is characterized by dermatologic lesions, brittle hair, fragile or black fingernails, metallic taste, dizziness, and nausea.

Description

Free radicals are naturally produced in the body through the normal metabolism of amino acids and fats. These free radicals are unstable molecules that can freely react with and destroy healthy cells. They can bind to and alter the structure of DNA thus leading to mutations and eventually to cancer. Besides cancer, this oxidative stress on the cells can lead to heart, eye, and neurological diseases.

Glutathione, lipoic acid, and CoQ10 are antioxidants formed naturally by the body but their levels decline with age. Vitamins C and E are necessary antioxidants but not produced by the body and must be obtained from the diet. The most common antioxidants are the vitamins A, C, and E. Additional antioxidants are natrol, found in grapes and wine; selenium; and melatonin. Flavonoids consist of a large family of antioxidant compounds found in fruits and vegetables. Among the well-studied flavonoids in terms of **cancer prevention** are catechins from green tea, genistein from soy, curcumin from turmeric, anthocyanosides from blueberries, and quercetin from yellow vegetables. More recent studies have added clack beans to the list of foods high in antioxidants and a 2003 study in Rome reported that women who ate dark chocolate showed some antioxidant benefits.

Although controversy will surround the topic of supplemental antioxidants for some time, there is little if any controversy that dietary levels of antioxidants are useful in preventing cancer. Because of this evidence, the American Cancer Society suggests five servings of fruits and vegetables each day.

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Antiviral therapy

Definition

Antiviral therapy is often used by cancer patients to treat viral infections. Commonly used antiviral medications include acyclovir, famciclovir, ganciclovir, valacyclovir, and foscarnet.

Description

Viral infections occur in almost all people at some time in their lives. The common cold is the most easily recognizable example of a virus that can be unpleasant but generally does not cause serious problems. For people with cancer, however, viruses can often cause life-threatening illnesses.

Viral infections in cancer patients can be much more serious and debilitating than in patients without cancer. Cancer patients will often have weakened immune systems from **chemotherapy** or from the cancer itself. Cancer patients who have bone marrow transplants are at especially high risk for life-threatening viral infections. Immediately after the transplant, the patient will have very few, if any, white blood cells, which are the body's main infection fighters. Viral infections such as **herpes simplex** virus (HSV), **herpes zoster** virus (HZV), and cytomegalovirus are often seen in cancer patients, and all can cause serious, life-threatening infections.

Until the development of the antiviral drug acyclovir 1974, no relatively safe and effective anti-viral medications for cancer patients were available. By the mid-1980s, acyclovir was being routinely used for cancer patients with herpes infections. Besides treating the infection itself, acyclovir can be taken on a daily basis to prevent infection from occurring. This can be especially important in people with very depressed immune systems, such as cancer patients who have undergone a bone marrow transplant.

Since the introduction of acyclovir, other anti-viral medications have been developed that have been very useful in the treatment of viral illnesses. For reasons that are still unknown, certain herpes infections in certain cancer patients do not respond to acyclovir. Fortunately, two other newer medications similar to acyclovir, called famciclovir and valaciclovir, are helpful in treating herpes infections, especially ones that are resistant to acyclovir.

While antiviral drugs such as acyclovir have made a large difference in treating herpes infections in cancer patients, there are other viral infections that do not respond to acyclovir. Cytomegalovirus is a common viral infection among cancer patients, and especially common among cancer patients who have had bone marrow transplants. Some antiviral medications like acyclovir are not effective against cytomegalovirus. Fortunately, two other antiviral medications known as ganciclovir and foscarnet are both effective against cytomegalovirus.

Recommended dosage

The recommended dosage for the various antiviral medications can vary considerably, depending on the health of the patient and how the medication is administered. For the treatment of herpes simplex and herpes zoster, the drugs acyclovir, famciclovir, and valacyclovir can be used. The recommended oral dosage ranges from 500 mg twice a day for valacyclovir, 500 mg three times a day for famciclovir, to 800 mg every four hours for acyclovir. There is also a formulation for the drug to be given administered though the vein. The dose for injection is different than the dose for oral therapy.

For the treatment of Cytomegalovirus, ganciclovir or foscarnet can be used. Both medications are generally given intravenously, although there is an oral formulation available for ganciclovir. The dosage is 5 mg per kg of body weight every 12 hours for 14 to 21 days, followed by maintenance therapy at a dose of 5 mg per kg per day as a single daily dose. The dosage for foscarnet ranges from 40 mg per kg to 90 mg per kg, depending on the diagnosis.

Precautions

The drugs acyclovir, famciclovir, valcyclovir, ganciclovir and foscarnet should all be used with caution by patients with kidney problems. With higher doses of these drugs, patients who do have kidney problems should have their kidney functioning monitored closely on a daily basis. The dosage is usually decreased depending on the degree of decreased kidney function. Kidney failure has been reported in patients taking high doses of foscarnet.

Ganciclovir should be used with extreme caution in women who may be pregnant, since it is teratogenic (causes abnormalities), as well as toxic, to developing embryos. There are no well-controlled studies of the other antiviral agents in pregnant women and it is not known whether these agents are excreted in breast milk. Therefore, it is not recommended that these antiviral agents be given to pregnant or nursing mothers unless the benefit outweighs the risk.

Side effects

Side effects common to all the antiviral medications include nausea, vomiting, **diarrhea**, headaches, and dizziness, rash, and decreased kidney function. Of the drugs

KEY TERMS

Herpes simplex virus—An infectious, contagious viral disease, caused by herpes simplex virus type one or two. It is characterized by fluid-filled lesions that can recur.

Herpes zoster virus—An acute, infectious viral disease, characterized by painful, fluid-filled lesions.

Cytomegalovirus—A viral disease caused by a herpes virus, generally rare but often seen in cancer patients. It can cause life-threatening pneumonia as well as blindness.

Teratogenic—Causes abnormalities to occur in developing embryos.

Gout—A condition, most often occurring in men, caused by a buildup of uric acid crystals deposited in joints, commonly the big toe.

used to treat herpes simplex, acyclovir seems to have more reported side effects than the other medications.

The two drugs that are used to treat cytomegalovirus, ganciclovir and foscarnet, have very different side effect profiles. Ganciclovir's major side effect is the lowering of white blood cells, a condition known as **neutropenia**. Because of this, a patient on ganciclovir should have their white blood cell count monitored closely. Foscarnet, while generally not causing a marked decrease in white blood cells, can cause sudden kidney failure. Patients who are taking foscarnet should make sure they maintain their fluid intake and have their kidney functions monitored closely.

Interactions

The antiviral drugs used to treat herpes simplex and zoster should be used with caution with other drugs that cause kidney problems. Also, they all interact with probenecid, a medication commonly used to treat gout.

Drug interactions with foscarnet and ganciclovir are more numerous and potentially dangerous. Both, especially foscarnet, must be used with caution with other drugs that cause kidney problems. Both must also be used with caution with other medications that lower seizure thresholds. Patients should notify their physician or consult with their pharmacist prior to starting any over the counter or herbal medications due to the numerous drug interactions that can occur with these agents.

Edward R. Rosick, DO, MPH, MS

Aromatase inhibitors

Definition

Aromatase inhibitors are a class of hormone drugs. They inhibit aromatase, an enzyme that regulates the production of estrogen.

Purpose

The aromatase inhibitors decrease blood and tumor levels of estrogen in postmenopausal women. They once were used only to treat advanced forms of **breast cancer** in postmenopausal women. Antiestrogens, such as tamoxifen, were the favored hormonal treatment choice for breast cancer. However, in late 2003, research began to show that aromatase inhibitors may work as effectively as tamoxifen with fewer side effects. In addition, aromatase inhibitors also were being considered for preventing other estrogen-dependent cancers such as endometrial cancer.

Description

Aromatase inhibitors lower a postmenopausal woman's estrogen levels, thereby preventing the cancer cells that are dependent on estrogen from growing.

Anastrazole (trade name Arimidex)

Anastrazole is a non-steroidal aromatase inhibitor that lowers blood levels of estradiol to prevent the rapidly growing cancerous cells. It is usually used in postmenopausal women as a treatment for advanced breast cancer that has not responded to other therapies, or it can be used as first-line therapy in breast cancer patients.

Exemestane (trade name Aromasin)

Exemestane is an aromatase inhibitor that reduces the concentration of estradiol in the bloodstream. It is also called an aromatase inactivator because it inactivates aromatase irreversibly, potentially providing continued benefits after treatment is stopped. It is used to treat advanced breast cancers in postmenopausal women whose cancers have not responded to other antiestrogen therapies.

Letrozole (trade name Femara)

Letrozole is a non-steroidal aromatase inhibitor that lowers blood estrogen levels by hindering the conversion of androgens to estrogens. It is used in postmenopausal women with advanced breast cancer that has progressed while on other antiestrogen therapy.

Recommended dosage

- Anastrazole: The adult dose is 1 mg a day by mouth
- Exemestane: The adult dose is 25 mg a day by mouth, after a meal
- Letrozole: The adult dose is 2.5 mg a day by mouth

Precautions

Aromatase inhibitors are not used in pregnant women because of the risk to the fetus. Since these drugs are generally prescribed for postmenopausal women, pregnancy is not usually an issue.

Except in life-threatening conditions, anastrazole, exemestane, and letrozole are not used in pregnancy because of risks to the fetus. These drugs should be avoided by people allergic to them and by nursing mothers.

Side effects

The aromatase inhibitors are generally tolerated well. Side effects are similar to the effects of decreased estrogen, such as hot flashes. People should report any side effects to the doctor.

Anastrazole

Rash is the most common side effect of anastrazole. Less common side effects include:

- hot flashes
- headache, light-headedness, dizziness, confusion
- depression, insomnia, anxiety
- chest pain, high blood pressure, obstruction of blood vessels
- **nausea and vomiting**, **diarrhea**, constipation, abdominal pain
- dry mouth, altered taste, appetite loss
- vaginal bleeding, vulvar itching
- hair thinning
- bone pain, tumor pain, weakness, muscle aches
- cough, sinusitis
- abnormally low red blood cell levels (**anemia**)
- abnormally low white blood cell counts (leukopenia)

Exemestane

Side effects include:

- hot flashes
- headache, **fatigue**, insomnia
- depression, anxiety
- high blood pressure
- nausea, vomiting
- increase in appetite
- diarrhea, constipation, abdominal pain
- cough, difficulty breathing

Letrozole

Common side effects include:

- headache
- nausea, vomiting
- lethargy
- appetite loss (**anorexia**)
- rash, itching

Less common side effects include:

- drowsiness, dizziness
- depression, anxiety
- high blood pressure
- constipation, diarrhea, heartburn
- hair loss
- hot flashes, sweating
- cough, difficulty breathing

KEY TERMS

Estradiol—A steroid that has some of the properties of estrogen.

Interactions

Patients who are taking any kind of prescription drug, over-the-counter drug, or herbal remedy should notify their physician before beginning any treatment with aromatase inhibitors.

See also Megestrol acetate; Tamoxifen.

Resources

PERIODICALS

Lewis, Jilene. "Breast Cancer Guidelines Suggest Alternative to Standard Therapy." *Drug Topics* August 18, 2003: 22.

Mitwally, Mohamed F., and Robert F. Casper. "Preventing Breast Cancer with Aromatase Inhibitors." *Contemporary OB/Gyn* December 2003: 68–77.

Rhonda Cloos, R.N.
Teresa G. Odle

KEY TERMS

Antineoplastic—A substance used to help prevent tumor growth.

Arsenic trioxide

Definition

Arsenic trioxide, also known by the trade name Trisenox, is an antitumor agent used for a specific type of leukemia known as acute promyelocytic leukemia.

Purpose

Arsenic trioxide is used to treat acute promyelocytic leukemia in patients who have not responded to standard treatment.

Description

Arsenic trioxide, like many other antineoplastic (antitumor) agents, acts by interfering with the growth of cells. Unfortunately, these drugs affect the growth of normal cells and tumor cells. In some patients the drug may have to be discontinued because normal cell growth is too severely affected. For example, a patient taking a large dose of arsenic trioxide might see tumor growth stop. However, the dosage might be high enough to also stop the body's normal growth of platelet cells. The loss of platelets might cause severe internal bleeding–a consequence more immediately toxic than the tumor.

Recommended dosage

Doses vary from individual to individual and depend on body weight as well as other medications the patient is taking. For acute promyelocytic leukemia dosages for adults and children five years of age and older are up to 60 injections of 0.15 mg/kg of body weight until bone marrow remission occurs.

Precautions

Arsenic trioxide has been shown to cause fetal abnormalities and miscarriage in animals. Women who might become pregnant should take precautions to ensure they do not become pregnant while taking this drug. Women who are nursing their infants should discontinue nursing while this medication is in their system.

Patients with bone marrow problems, heart problems, kidney problems, or low levels of magnesium or potassium in the blood should notify their physician before taking any of this medicine. Patients should notify their physician of any illnesses they may have before taking arsenic trioxide.

Because persons taking arsenic trioxide may have decreased immunity, it is important for them to avoid infection. Caution should be taken to avoid unnecessary exposure to crowds and people with infections.

Patients may experience unusual or excessive bruising and/or bleeding and should avoid situations in which it is likely they could cut or bruise themselves. Patients should consult their physician immediately if they have any indication of excessive bleeding or bruising, including black and tarry stools, blood in the urine or stools, unusual bleeding or bruising, pinpoint red marks on their skin, vomit containing blood or what appears to be coffee grounds (dried blood). Severe symptoms may indicate a medical emergency.

Side effects

Symptoms include unusual heartbeat (fast, slow, irregular, or pounding), chest pain, high blood pressure, trouble breathing, bluish lips, skin, palms, or skin underneath the fingernails, muscle cramps, numbness or tingling, headache, acting or feeling drunk, confusion, fainting, dizziness, eye pain, blurred vision, excessive weakness, excessive **fatigue**, or excessive drowsiness.

Patients should also contact their physician immediately if they experience a fruity odor in their mouth, a dry mouth, excessive sweating, flushing, urine retention, excessive urination, increased appetite or thirst, abdominal pain, loss of appetite, unexplained weight gain or loss, or severe nausea.

Patients may have vomiting, nausea, **diarrhea**, insomnia, sour stomach, heartburn, constipation, gas, neck pain, back pain, **bone pain**, bloating, swelling, pain or swelling at the injection site, joint, muscle, or limb pain, **depression**, or nosebleeds.

Patients should always notify their physician about any unusual symptoms they experience while on medication.

Interactions

Patients should tell their doctors if they have a known allergic reaction to arsenic trioxide or any other medications or substances, such as foods and preservatives. Before taking any new medications, including nonprescription medications, **vitamins**, and herbal medications, the patients should notify their doctors.

Michael Zuck, Ph.D.

Arteriography, Angiogram *see* **Angiography**

Ascites

Description

Ascites is defined as an excessive amount of fluid built up within the peritoneal cavity. Both the abdominal organs and the abdomen itself are lined with membranes called the peritoneum. Between these two linings is a space referred to as the peritoneal cavity. In pathological conditions that result in edema, or excessive fluid accumulation in bodily tissues, fluid can build up in the peritoneal cavity.

Smaller abdominal fluid amounts usually do not produce symptoms. However, larger accumulations can cause:

- rapid weight gain
- abdominal discomfort and distention
- shortness of breath and actual dyspnea, or difficulty breathing
- swollen ankles

Severe cases of ascites can result in the retention of literally gallons (each gallon equals nearly four liters) of liquid in the peritoneal cavity. If fluid retention is sufficiently severe, the abdomen becomes swollen and even painful. Breathing can be affected as the fluid-filled peritoneal cavity presses upon the diaphragm, a very necessary component of respiration. The diaphragm is made up of a dome-shaped sheet of muscles that separates the thoracic, or chest, cavity from the abdomen. When the muscle fibers of the diaphragm contract, the space in the chest cavity is enlarged, and air enters the lungs to fill the enlarged space. When pressure on the diaphragm from fluid build-up occurs, it lessens the ability of these diaphragm muscular fibers to expand and contract, and results in impaired breathing.

Ascites, in itself, is not a disease, but rather a symptom of several other pathological conditions. These include:

- Cirrhosis of the liver, which is responsible for 80% of all instances of ascites in the United States.
- Pancreatic ascites develops when a cyst that has thick, fibrous walls (pseudocyst) bursts and permits pancreatic juices to enter the abdominal cavity.
- Chylous ascites, which has a milky appearance caused by lymph that has leaked into the abdominal cavity. Although chylous ascites is sometimes caused by trauma, abdominal surgery, tuberculosis, or another peritoneal infection, it is usually a symptom of **lymphoma** or some other cancer.
- Cancer causes 10% of all occurrences of ascites in the United States. It is most commonly a consequence of disease that originates in the peritoneum (peritoneal carcinomatosis) or of cancer that spreads (metastasizes) from another part of the body. Tumors especially prone to malignant ascites formation include **ovarian cancer** and metastatic gastrointestinal tumors.
- Endocrine and renal ascites are rare disorders. Endocrine ascites, sometimes a symptom of an endocrine system disorder, also affects women who are taking fertility drugs. Renal ascites develops when blood levels of albumin dip below normal. Albumin is the major protein in blood plasma. It functions to keep fluid inside the blood vessels.

Causes

The two most important factors in the production of ascites due to chronic liver disease are low levels of albumin in the blood and an increase in the pressure within the branches of the portal vein that run through liver (portal hypertension). Low levels of albumin in the blood cause a change in the pressure necessary to prevent fluid exchange (osmotic pressure). This change in pressure allows fluid to seep out of the blood vessels. The scarring that occurs in cirrhosis causes portal hypertension. Blood that cannot flow through the liver because of the increased pressure leaks into the abdomen and causes ascites.

Other conditions that contribute to ascites development include:

- hepatitis
- heart or kidney failure
- inflammation and fibrous hardening of the sac that contains the heart (constrictive pericarditis)

Persons who have systemic lupus erythematosus but do not have liver disease or portal hypertension occa-

sionally develop ascites. Depressed thyroid activity sometimes causes pronounced ascites, but inflammation of the pancreas (pancreatitis) rarely causes significant accumulations of fluid.

Treatments

Reclining minimizes the amount of salt the kidneys absorb, so treatment generally starts with bed rest and a low-salt diet. Urine-producing drugs (diuretics) may be prescribed if initial treatment is ineffective. The weight and urinary output of patients using diuretics is normally carefully monitored, often on a daily basis. This scrutiny involves watching for signs of:

- Hypovolemia (massive loss of blood or fluid) that can often result in drastic drops in blood pressure.
- Azotemia (abnormally high blood levels of nitrogen-bearing materials).
- Potassium imbalance that can result in cardiac arrhythmia.
- High sodium concentration. Sodium should be restricted from the diet as much as possible.

Because of the discomfort and respiratory difficulty moderate-to-severe accumulations of fluid can produce, fluid removal, or **paracentesis**, is often the treatment of choice. Paracentesis involves the extraction of fluid from the abdominal cavity via a needle that is usually inserted into the peritoneum under local anesthesia. This is a relatively safe and painless method of relieving fluid build-up. It is considered safer than diuretic therapy, resulting in fewer complications and requiring shorter hospital stays.

Large-volume paracentesis is also the preferred treatment for massive ascites. Diuretics are sometimes used to prevent new fluid accumulations, and the procedure may need to be repeated periodically.

In cases of ascites that do not respond appropriately to the treatments described above, a **peritoneovenous shunt** may be inserted. This device is equipped with a one-way valve that allows fluid from the peritoneal cavity to pass into the venous blood circulatory system. From there the fluid is eliminated by the kidneys. In cases of malignant ascites, there is a concern that the use of such a shunt could enhance the spread of the cancer. This relatively small risk must be balanced against the positive effect the shunt can have on the individual's quality of life as well as against his or her expected survival period.

Alternative and complementary therapies

Dietary alterations, focused on reducing salt intake, are an important facet of treatment. Potassium-rich foods like low-fat yogurt, mackerel, cantaloupe, and baked potatoes help balance excess sodium intake and help ensure proper heart function. Such complementary therapies should always be considered an adjunct to, not a substitute for, the conventional treatments described above.

Resources

PERIODICALS

Bieligk, S.C., B.F. Calvo, and D.G. Coit. "Peritoneovenous Shunting for Nongynecologic Malignant Ascites." *Cancer* 91, no. 7 (April 2001): 1247–9.

ORGANIZATIONS

National Cancer Institute, National Institute of Health. 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. <http://www.nci.nih.gov>.

Joan Schonbeck, R.N.

Asparaginase

Definition

Asparaginase (also known as L-asparaginase, and sold under the brand name Elspar) is a medicine used to stop growth of cancer and formation of new cancer cells.

Purpose

Asparaginase is used as part of an induction regimen for the treatment of **acute lymphocytic leukemia** (ALL) in children.

Description

Asparaginase is an enzyme made from the bacteria *escherichia coli* (E. coli). In this country, two forms of asparaginase are available: one made from E. coli, and a slightly changed version of the E.Coli form linked to polyethylene glycol (PEG) molecule. This PEG-linked asparaginase is called **pegaspargase**. This version was made available in 1994, is more expensive than the other form, and is mainly used in patients who have developed an allergy to E. Coli. Another natural form of asparaginase made from the plant bacteria *erwinia carotovora* is known by the brand name Erwinar and can be specially obtained for patients who develop a severe allergy to E. coli asparaginase. Asparaginase kills cancer cells by depleting a certain protein in the blood (L-asparagine) that is necessary for survival and growth of tumor cells in patients with ALL. Fortunately, normal cells are not dependent on L-asparagine for survival.

Asparaginase is mainly given in combination with **vincristine** and steroids (either prednisone or **dexamethasone**) for the first three weeks of therapy.

Recommended Dosage

Adults and children

INDUCTION CHEMOTHERAPY FOR ALL Doses vary between different **chemotherapy** protocols. The usual dose is 6,000-10,000 units per square meter of body surface area given for 10 days. Patients should refer to individual protocol for recommended dose.

Administration

This medicine can be given directly into the muscle (intramuscular) or into the vein (intravenous). Intramuscular injection of asparaginase lowers the risk of severe allergic reactions (also known as hypersensitivity or anaphylaxis). The risk of hypersensitivity reaction is higher with the second and third dose of the drug.

Precautions

The use of this medication should be avoided in patients with active pancreatitis (inflammation of the pancreas) or history of pancreatitis, and in patients with serious allergic reaction to asparaginase in the past.

Asparaginase should only be given in a hospital. A patient's blood pressure will need to be monitored every 15 minutes for the first hour. A small test dose may be given to check if patient is allergic to this medicine.

This medication can lower the body's ability to fight infections. Patients should avoid contact with crowds or any individual that may have an infection.

Breast-feeding mothers should use asparaginase with caution. It is not yet known whether this drug crosses into breast milk. Women who are pregnant or may become pregnant should avoid this drug unless the benefits to the mother outweigh the risks to the child.

Contact a doctor immediately if any of these symptoms develop:

- **fever**, chills, sore throat
- yellowing of the skin or eyes
- puffy face, skin rash, trouble breathing, joint pain
- drowsiness, confusion, hallucinations, convulsions
- unusual bleeding or bruising
- stomach pain with nausea, vomiting and loss of appetite

KEY TERMS

Acute lymphocytic leukemia (ALL)—This is the most common cancer in children. Patients with ALL can present with fever, weakness, fatigue, pallor, unusual bleeding and easy bruising, pinpoint dots on the skin, large lymph nodes, large liver and spleen. ALL in children has a much better prognosis than in adults, with over 90% of children going into remission and an 80% cure rate with chemotherapy.

Anaphylaxis—An immediate kind of an allergic reaction that usually happens after a second exposure of a body to a drug, toxin, or some types of foods. A person may experience a dangerous drop in blood pressure, skin rash, itching, puffiness of the face, and difficulty breathing. Anaphylaxis is a medical emergency and can result in death.

Induction therapy—The first stage in treatment of ALL. The purpose of this stage is to quickly cause remission of the disease. The combination of vincristine, asparaginase, and steroids make up the foundation of induction regimen.

A physician will perform blood tests before starting therapy and during therapy to monitor complete blood count, blood sugar, and pancreas, kidney, and liver functions.

Side effects

Asparaginase is a very potent medicine that can cause serious side effects. An allergic reaction with skin rash, **itching**, joint pain, puffy face, and difficulty breathing can occur very quickly after injection with his drug. This side effect is managed by having the drugs epinephrine, **diphenhydramine**, and steroids available near the bedside to counter the allergic reaction if it occurs. Other common side effects include nausea, vomiting, **diarrhea**, loss of appetite, stomach cramps, and yellowing of the eyes or skin. Less frequent side effects include high blood sugar, drowsiness, confusion, hallucinations, convulsions, decreased kidney function, increased blood clotting, mouth sores, and decreased ability to fight infections. Usually the side effects of asparaginase are more severe in adults than in children.

Interactions

Asparaginase can decrease effectiveness of **methotrexate** in killing cancer cells when given right before

and together with methotrexate. The use of these two medicines together should be avoided.

Asparaginase can decrease breakdown and increase toxicity of **cyclophosphamide**.

Risk of liver disease may be increased in patients receiving both asparaginase and **mercaptopurine**.

This medicine can increase blood sugar especially when given in together with steroids.

Asparaginase should be given after vincristine instead of before or with vincristine because it can increase the risk of numbing, tingling and pain in hands and feet.

Olga Bessmertny, Pharm.D.

Astrocytoma

Definition

Astrocytoma is a tumor that arises from astrocytes, star-shaped cells that play a supportive role in the brain.

Description

The brain acts as a computer that controls all of the functions of the body. It stores information, memories, and with the use of hormones and electrical impulses, regulates and sends instructions to the rest of the body. Because of the brain's importance, cancers in the brain can affect many of the body's functions. The location of a tumor within the brain determines which effects it will have. Astrocytomas may occur in the cerebrum, the site of thought and language, the cerebellum, the area responsible for movement and muscle co-ordination, or the brainstem, the location that regulates critical activities like breathing and heartbeat. Childhood astrocytomas are most commonly located in the cerebellum, while adults usually develop astrocytoma in the cerebrum.

Astrocytomas rarely metastasize (spread) outside the brain to other parts of the body; however, they may grow and spread within the brain. As there is no extra room in the skull, the presence of a brain tumor causes an increase in intracranial (within the skull) pressure, resulting in headaches and possibly affecting normal brain function by compressing delicate brain tissue.

Astrocytomas are a type of glioma, a tumor of glial cells (specialized cells that give physical support and electrical insulation between neurons). They are sometimes called gliomas, anaplastic astrocytomas, or glioblastoma multiforme. Oligoastrocytomas are a type of mixed glioma similar to astrocytomas. They usually contain cells that originate from oligodendrocytes as well as astrocytes, and are usually low grade (grading is an estimate of the tumor's malignancy and aggressiveness; lower-grade tumors require less drastic therapy than high-grade tumors).

Demographics

Astrocytoma occurs slightly more often in males than in females. It is also slightly more common in Caucasians than in those of African or Asian descent. Although it affects both adults and children, children usually develop a less serious form with a better prognosis. The total incidence of all types of brain cancer, including astrocytomas, is approximately 13 people out of every 100,000.

Causes and symptoms

The cause of astrocytoma is not known. Brain cancer may occasionally be caused by previous radiation treatments; however, x rays are not believed to play a role. As of 2001, studies have indicated that the moderate use of handheld cellular phones does not cause brain cancer; ongoing research will determine if long-term cellular phone use causes an increase in cancer incidence.

Some studies suggest that brain tumors may occur more frequently in people who have occupational exposure to certain chemicals, including some pesticides, formaldehyde, vinyl chloride, phenols, acrylonitrile, N-nitroso compounds, polycyclic aromatic hydrocarbons, lubricating oils, and organic solvents. The greatest risk is associated with exposure before birth or during infancy.

There is a slightly higher incidence of astrocytoma in the siblings and parents of people with this tumor; however, only one type of astrocytoma is known to have a genetic cause. The rare subependymal giant cell astrocytoma occurs in conjunction with tuberous sclerosis, a hereditary disorder.

A wide variety of symptoms develop as a result of astrocytoma including the following:

- headache
- **nausea and vomiting**
- neck stiffness or pain
- dizziness
- seizures
- unsteadiness in walking or unusual gait

- lack of coordination, decreased muscle control
- visual problems such as blurring, double vision, or loss of peripheral vision
- weakness in arms or legs
- speech impairment
- altered behavior
- loss of appetite

Because there are several different types of astrocytoma, not all patients will show the same symptoms. The location of the tumor within the brain will determine which symptoms a patient will experience. Because the tumor causes an increase in intracranial pressure, most people with astrocytoma will develop headaches and nausea and vomiting.

Diagnosis

In the first stage of diagnosis the doctor will take a history of symptoms and perform a basic neurological exam, including an eye exam and tests of vision, balance, coordination and mental status. The doctor will then require a computerized tomography (CT) scan and **magnetic resonance imaging** (MRI) of the patient's brain. During a CT scan, x rays of the patient's brain are taken from many different directions; these are combined by a computer, producing a cross-sectional image of the brain. For an MRI, the patient relaxes in a tunnel-like instrument while the brain is subjected to changes of magnetic field. An image is produced based on the behavior of the brain's water molecules in response to the magnetic fields. A special dye may be injected into a vein before these scans to provide contrast and make tumors easier to identify.

If a tumor is found it will be necessary for a neurosurgeon to perform a **biopsy** on it. This simply involves the removal of a small amount of tumor tissue, which is then sent to a neuropathologist for examination and staging. The biopsy may take place before surgical removal of the tumor or the sample may be taken during surgery. Staging of the tumor sample is a method of classification that helps the doctor to determine the severity of the astrocytoma and to decide on the best treatment options. The neuropathologist stages the tumor by looking for atypical cells, the growth of new blood vessels, and for indicators of cell division called mitotic figures.

Treatment team

Treatment of astrocytoma will involve a neurosurgeon to remove the tumor, a neuropathologist to examine the tumor sample, and an oncologist to monitor the patient's health and coordinate **radiation therapy** and **chemotherapy** if necessary. Nurses and radiation therapists will also play a role. After treatment, the patient may be followed up by a neurologist to ensure that the tumor does not grow or recur.

Clinical staging, treatments, and prognosis

There are several different systems for staging astrocytomas. The World Health Organization (WHO) system is the most common; it has four grades of increasing severity based on the appearance of the astrocytoma cells. Other methods of staging correspond fairly closely to the WHO system. Grades I and II are sometimes grouped together and referred to as low-grade astrocytomas. Over time, tumors may progress from a low-grade form with a relatively good prognosis to a higher-grade form and poorer prognosis. Additionally, tumors may recur at a higher grade.

Grade I Pilocytic Astrocytoma

This is also sometimes referred to as juvenile astrocytoma because it occurs more frequently in children than adults. Under a microscope, the astrocytes are thin and elongated, and known as pilocytes. They are accompanied by Rosenthal fibers. The tumor mass does not invade surrounding tissues and is sometimes enclosed in a cyst. In children, pilocytic astrocytoma often occurs in the cerebellum, but may also occur in the cerebrum.

Treatment of this grade depends on the patient's age and the location of the tumor. Surgery is the preferred treatment for this type of astrocytoma; it is performed by a procedure known as a **craniotomy**. An incision is made in the skin and an opening is made in the skull. After the tumor is removed, the bone is normally replaced and the incision closed. The neurosurgeon may also insert a shunt (drainage system) to relieve intracranial pressure; this involves inserting a catheter into a cavity inside the brain called a ventricle, then threading the other end under the skin to a drainage area where the fluid is absorbed.

If the tumor can be completely surgically removed, the patient may not need further therapy and may be monitored only for recurrence. If the tumor cannot be completely removed, patients may be given chemotherapy as well. If the tumor is not completely resected or if it continues to grow after chemotherapy, radiation therapy may be necessary. Radiation therapy is not normally given to children under the age of three in order to prevent permanent damage to the child's healthy brain tissue. Radiation treatment may cause swelling in the brain; steroids may be prescribed to reduce the swelling.

The best indicator for prognosis is complete removal of the tumor. With complete tumor removal, 80% of patients are alive ten years later. Location of the tumor in the cerebellum also suggests a better prognosis than other locations.

Grade II Low-Grade Diffuse Astrocytoma

These astrocytomas spread out and invade surrounding brain tissues but grow very slowly. Under the microscope, fibrous structures are present. Grade II astrocytomas may occur anywhere in the brain, in the cerebellum and brain stem, or in the cerebrum, including the optic pathways. Genetic studies indicate that mutations of the tumor suppressor gene p53 occur frequently in these tumors.

Surgical removal of the tumor is the first choice for treatment, but it may not be possible due the tumor's location. Surgery is usually followed by radiation. Patients under 35 years of age have a better prognosis than older patients; in older patients, low-grade tumors progress to higher grades more rapidly. Overall median survival is four to five years.

Pleimorphic xanthoastrocytoma, a tumor originating in cells of a mixture of glial and neuronal origin, is often considered a grade II astrocytoma. It is relatively benign and treated only with surgery.

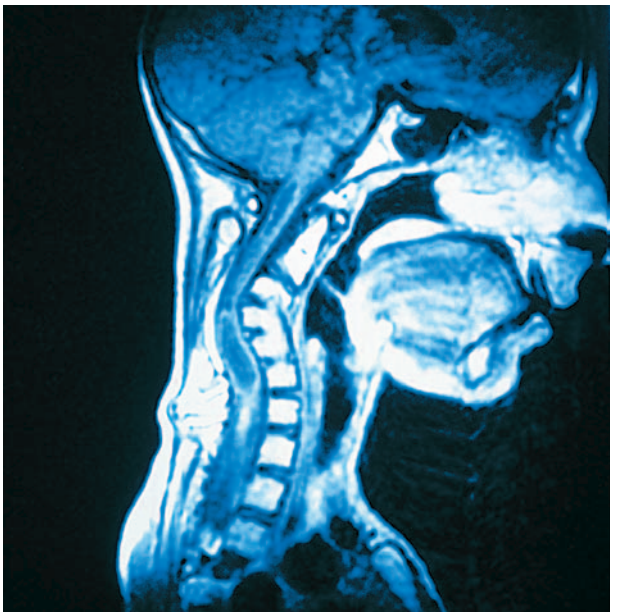
Grade III Anaplastic Astrocytoma

Anaplastic astrocytoma occurs most frequently in people aged 50 to 60. The term anaplastic means that the cells are not differentiated; they have the appearance of immature cells and cannot perform their proper functions. Researchers believe this is due to a gradual accumulation of genetic alterations in these cells. These tumor cells invade surrounding healthy brain tissue.

Anaplastic astrocytomas may be inoperable because of their location and their infiltration into normal tissue; in this case radiation therapy is recommended. Chemotherapy may include various combinations of alkylating agents and other drugs, including **carmustine**, **cisplatin**, **lomustine**, **procarbazine** and **vincristine**. These tumors tend to recur more frequently than grade I and II tumors. Following treatment, median survival is 12 to 18 months. The five-year survival rate for these patients is approximately 10% to 35%.

Grade IV Glioblastoma Multiforme

Glioblastoma Multiforme (GBM) is the most common primary brain tumor in adults. These tumors aggressively invade adjacent tissue and may even spread throughout the central nervous system. They frequently occur in the frontal lobes of the cerebrum. Tumor biopsies may show large areas of necrosis, or dead cells, surrounded by areas of rampant growth. There may also be a mixture of cell types within the biopsy. Genetic studies show that a number of different types of mutations can take place in genes for tumor suppressor p53 and other proteins that play a role in controlling the normal growth of cells.



Magnetic resonance image (MRI) of the head and neck of a 15-year-old boy showing the recurrence of an astrocytoma of the spinal cord. The tumor appears about halfway down the neck. *(Copyright Simon Fraser, Neuroradiology Dept., Newcastle General Hospital, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Often GBM cannot be entirely surgically removed because it affects large areas of the brain. Radiation therapy will be given regardless of whether surgery is possible, except to very young children. Conventional radiation may be performed, but more specialized types, such as stereotactic radiosurgery, which uses imaging and a computer to treat the tumor very precisely, or interstitial radiation, which delivers radiation by placing radioactive material directly on the tumor, may also be used. Chemotherapy will follow radiation; it may include carmustine, lomustine, procarbazine, and vincristine.

GBM is most common in patients over 50 years of age and rarely occurs in patients under 30. Increasing age is associated with a poorer prognosis. Median survival is 9 to 11 months following treatment. Fewer than 5% of patients are alive five years later. Because of the poor prognosis of GBM, it is treated more aggressively

than low-grade astrocytomas; many **clinical trials** take place to test new treatments.

Alternative and complementary therapies

While no specific alternative therapies have become popular for this particular type of brain cancer, patients interested in pursuing complementary therapies should discuss the idea with their doctor. A doctor may be able to provide information about the efficacy of certain techniques and whether they may interfere with conventional treatment.

Coping with cancer treatment

Patients may experience unpleasant side effects due to their treatment. Patients should discuss any side effects they experience with their doctors; occasionally an effect may be unexpected or dangerous and dosages may need to be adjusted. Doctors can help alleviate nausea with antinausea medications and may prescribe antidepressants to help the patient deal with the cancer on a psychological level. Joining support groups will also help patients deal with the psychological effects of treatment. Cancer survivors can help provide encouragement and offer advice for coping with cancer on a day-to-day basis.

Clinical trials

Clinical trials are an important treatment possibility, especially for patients with tumors that are inoperable or do not respond well to treatment. Participation in clinical trials also gives patients an opportunity to make contributions to the search to find a cure for their cancer. A wide variety of clinical trials are available, particularly for the higher-grade astrocytomas. Trials for higher-grade astrocytomas may test new drugs, new combinations of drugs, drug implants, and higher doses of drugs, possibly in combination with different methods of radiation therapy. Some studies may examine the use of gene therapy or immune therapy, including **vaccines**.

Trials for lower-grade astrocytomas focus on finding chemotherapy that causes fewer side effects. Some studies may also feature new combinations of drugs while others may attempt to treat the tumor by using lower dosages of drugs spread out over a longer period of time.

Prevention

Currently, scientists do not know what causes the majority of brain cancers. There may be a slight genetic predisposition, as family members of astrocytoma patients have a slightly increased incidence of the disease. Clinical studies show that a large number of genetic alterations take place in the higher grade astrocytomas; although this helps to explain what is going wrong in the cells, it does not explain what is causing these genetic mutations to take place.

While it is known that ionizing radiation can cause brain tumors, most people are not exposed to this type of radiation unless they are being treated for cancer. Ongoing studies are examining the long-term risks of other types of radiation, but as of 2001, neither x rays, electromagnetic fields, or cellular phones appear to increase the likelihood of brain cancers.

Although evidence is not yet conclusive, some studies suggest that some brain tumors may be caused by environmental exposure to certain organic chemicals. Exposure is most harmful to the developing fetus and infants, so pregnant women may wish to consider whether they have any occupational exposure to organic chemicals. Parents of infants should be aware of pesticides and any other potentially harmful chemical their child could come into contact with.

Additionally there is some evidence that supplements containing **vitamins** A, C, E, and folate may have a protective effect when taken during pregnancy. The children of women who take these supplements during pregnancy are half as likely to develop brain tumors before age five.

Special concerns

Children who develop astrocytoma should be monitored regularly by their physicians to ensure that the tumor does not recur. A follow-up schedule should be discussed with the doctor; the child may be examined twice a year initially, then tested annually afterwards. In addition to the possibility of recurrence, other health problems due to treatment may arise in the child. The child may have lower levels of growth hormone or thyroid hormone or delayed growth as a result of radiation.

KEY TERMS

Anaplastic—Undifferentiated, appearing to have an immature cell type.

Biopsy—A sample of tissue taken from the tumor.

Glioma—A tumor of the brain's glial cells.

Primary tumor—An original tumor, not a metastatic tumor resulting from cancer's spread.

QUESTIONS TO ASK THE DOCTOR

- Where inside my brain is the cancer located and where will it spread?
- What types of treatment are recommended?
- What are the possible side effects of this treatment?
- How can the side effects be minimized?
- Am I eligible for any clinical trials?
- Are there any alternatives to this treatment?
- What are the chances that the cancer will return?
- Will this cause any disabilities?
- How will this affect my daily life?

There may also be decreased intellectual capacity or learning or physical disabilities that can be detected during follow-up. Parents can then arrange for rehabilitation or special education for their child.

Adults may also experience permanent negative effects as a result of their treatment. Radiation damage to healthy tissue may occasionally cause delayed effects such as decreased intellect, impaired memory, changes in personality, and confusion. These types of side effects should be reported to a health professional; the patient can be referred to rehabilitation specialists who can help with regaining abilities.

See also Brain and central nervous system tumors; Childhood cancers; Tumor grading.

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The Brain Tumor Society. 124 Watertown St., Suite 3-H, Watertown, MA 02472. (800) 770-8287. <http://www.tbts.org>.

National Brain Tumor Foundation. 414 13th St., Suite 700, Oakland, CA 94612-2603. (800) 934-2873. <http://www.braintumor.org>.

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Racquel Baert, M.S.

ATG, anti-thymocyte globulin *see* **Lymphocyte immune globulin**

Atropine *see* **Antidiarrheal agents**

Azacitidine

Definition

Azacitidine, is an antineoplastic (antitumor) agent that acts by interfering with the growth of cells.

Purpose

Azacitidine is a **chemotherapy** drug used primarily to treat adults and children with **acute myelocytic leukemia** that has not responded to traditional therapy. It is also used to treat myelodysplastic syndrome. There is limited data that azacitidine may be useful for chronic myelogenous leukemia, sickle cell anemia, and cancers that have spread to other organs in the body. It should also be noted that azacitidine does not appear on the FDA's approved drug list. Currently, azacitidine is prescribed only as an experimental drug.

Description

DNA can be thought of as the blueprint for the cell, and RNA as the messenger to carry out the instructions of the DNA. RNA, or ribonucleic acid, is a close relative of DNA, deoxyribonucleic acid. Both are made up of four different bases, adenine, guanine, cytosine, and thymine. Azacitidine pretends to be cytosine, and is incorporated into the RNA and DNA of cells, inhibiting them from carrying out their normal functions and causing cell death.

KEY TERMS

Gene—A functional unit of DNA.

Recommended dosage

The dose of azacitidine depends on the reason it is being administered and whether any other drugs are involved in treatment. The usual dose for azacitidine is 50 to 200 mg per square meter of body surface area per day for five to 10 days. This is repeated at two to three week intervals. Azacitidine is administered either through the vein or injected under the skin. It may be injected under the skin at a dose of 75 mg per square meter of body surface area per day for seven days, to be repeated every 4 weeks.

Precautions

Pregnant women should not take this drug, and should be aware that this drug has been shown to cause death or abnormality in the fetuses of laboratory animals. Women who might become pregnant while taking this medication should take steps to ensure that they do not. Nursing mothers should discontinue nursing while taking this medication. All patients should have this drug administered by a health care professional and their progress regularly monitored.

Side effects

The most common side effect of azacitidine is the decreased production of white blood cells, which are important in fighting infections, and platelets, which are important in preventing bleeding. Nausea, vomiting, and **diarrhea** are also very common with this drug.

Other side effects include **fever**, general muscle pain, weakness, and lethargy. Decreased liver function, low blood pressure, and changes in kidney function have also been reported with azacitidine. Also, injections of the drug under the skin can cause redness, swelling, or mild pain.

Interactions

Azacitidine has no known interactions with other drugs. However, prior to initiating any over-the-counter, herbal, or new medications, patients should consult their physician, nurse, or pharmacist to prevent possible drug interactions.

Michael Zuck, Ph.D.

Azathioprine

Definition

Azathioprine is a nonspecific immunosuppressant antimetabolite that can be used as a chemotherapeutic agent to inhibit lymphocyte purine metabolism. In the United States, azathioprine is also known by the brand name Imuran.

Purpose

In 1968 the Food and Drug Administration approved azathioprine for use after organ transplantation to decrease the chance of the body rejecting the transplanted organ. Azathioprine, however, is also an experimental drug that can be used during treatment of such cancers as leukemia and lymphoma. In the body, azathioprine is converted to **mercaptopurine** (6-MP) and thus has the same effects as that **chemotherapy** drug. They both are purine analogs that interfere with the metabolism of purine-based nucleotides found in DNA.

The use of azathioprine results in killing cells such as T-lymphocytes. This effect is important in treating such cancers as lymphocytic leukemia. The idea is that if T-lymphocyte reproduction is inhibited by interfering with DNA synthesis, then the cancer cell reproduction will also be inhibited. Certain types of leukemia and lymphoma are treated with radiation and chemotherapy, which destroy dividing cells such as those in the bone marrow. As a result, the patient is no longer able to produce blood cells. To combat the loss of blood cells, a bone marrow transplant may be performed to provide the patient with healthy marrow. The body may react against the foreign bone marrow. Therefore, an additional benefit of azathioprine use as an immunosuppressant could be to produce fewer white blood cells, thus interfering with the body's natural **immune response** to foreign proteins, such as those found on the cell surfaces of bone marrow coming from a bone marrow donor.

Because azathioprine has anti-inflammatory action, it is also used to treat such disorders of the digestive tract as irritable bowel disease (IBD) as well as the vasculitides, which are a group of disorders characterized by inflammation of blood or lymphatic vessels.

Description

Azathioprine is a derivative of mercaptopurine, a purine analog antimetabolite, which interferes with the enzymatic pathways for biosynthesis of nucleic acids by substituting for normal metabolites. In this way, it can act as an immunosuppressant by interfering with the production of white blood cells such as lymphocytes.

Recommended dosage

Azathioprine can be taken either orally (50 milligram scored tablets) or through an injection (100 milligram vials for intravenous use). Dosing is based on body weight and size of the patient. Initially, the oral dosage is approximately 3 to 5 milligrams per kilogram of body weight, while the injection dosage is approximately 1 milligram per kilogram of body weight. At time goes on, the physician may decrease the dosage. Patients can take this medicine in a single dose per day. The duration of treatment will continue until the fear of transplant rejection has passed.

Precautions

Since this medication is an immunosuppressant and results in a lower white blood cell count, there is a higher risk of developing infection. Therefore, patients using azathioprine should limit their contact with people that have existing infections, they should not have dental work done while on this medication, and they should not touch their eyes or inside of their nose unless they have just washed their hands. Patients should also take care not to cut themselves and should be careful when using a regular toothbrush and dental floss.

Although some early studies performed in animals stated that azathioprine should not be used during pregnancy, two groups of researchers in Italy and Canada respectively reported in 2004 that the drug has a very small potential for harm to the fetus. Moreover, although azathioprine can cross into breast milk, there is no evidence that the small amounts absorbed by a nursing infant are harmful.

Side effects

The most common and less serious side effects include **fatigue**, weakness, loss of appetite (**anorexia**), **nausea and vomiting**, and upset stomach. Upset stomach can be alleviated if azathioprine is taken with food or milk.

Other side effects may occur that require the attention of a medical professional. These include:

- cough or hoarseness
- **fever** or chills
- lower back or side pain
- extreme fatigue
- black tarry stools
- blood in the urine
- red spots on the skin
- fast heartbeat
- shortness of breath
- liver problems

Since the immune system is depressed when azathioprine is used, the result can be pancytopenia, including leukopenia and **thrombocytopenia** as well as macrocytic **anemia**. The severity of these is dependent on the dose, and the dose may be lowered by the physician as needed.

Azathioprine has been used in children and has not been shown to induce side effects different from those found in adults. However, as with many medications there have not been any specific tests done with the elderly. It is not expected to cause any different side effects from those encountered in younger adults.

Interactions

There are medications and other medical conditions that can interact with azathioprine. A medication called **allopurinol** is used to treat gout and can increase the effects and toxicity of azathioprine because it interferes with the removal of azathioprine from the body.

KEY TERMS

Analog—A chemical compound with a structure similar to another chemical, but differing in a certain way.

Antimetabolite—A drug that resembles a substance that occurs naturally in a metabolic pathway, interfering with metabolism.

Bone marrow—The soft tissue inside of bones that produces blood cells.

Gout—A form of arthritis that involves ureic acid.

Leukopenia—Decrease in the amount of white blood cells.

Lymphocytes—A type of white blood cell and part of the immune system.

Macrocytic anemia—Anemia where blood cells are much larger than normal.

Myelosuppression—Decrease in the proliferation of bone marrow cells.

Pancytopenia—Decrease in all the cellular components of the blood.

Purine—A base found in nucleotides and nucleic acids that are used to make DNA.

Vasculitis (plural, vasculitides)—Inflammation of blood or lymphatic vessels.

Both kidney disease and liver disease can increase the effects and toxicity of azathioprine. Both diseases interfere with the removal of azathioprine from the body. If the patient has either of these diseases, the physician may make adjustments in the dosage given.

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United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

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Aztreonam *see* **Antibiotics**

B

Bacillus Calmette Guérin

Definition

Bacillus Calmette Guérin, or BCG, is a genetically engineered bacterium that is used to treat **bladder cancer**. BCG also is known by the brand names ImmuCys, TheraCys and TICE BCG.

Purpose

Excision (cutting out) of bladder tumors can lead to extreme discomfort in patients because of the damage done to the bladder, the organ that collects and holds urine until it can be released from the body. In certain kinds of bladder cancers, treatment with BCG seems to cause cancers to shrink or disappear. Thus, when BCG treatment is effective, it is possible to preserve the bladder.

Description

BCG is made by altering the DNA, or hereditary material, of a bacterium. The bacterium that is altered is one that has been used for decades to vaccinate against tuberculosis. There are several different ways in which BCG has been modified by genetic engineering. In each case, however, the DNA added to the BCG from human cells gives instructions for the production of compounds that stimulate the immune system. The compounds are all proteins and are known by the scientific category name of cytokines.

Even BCG that has not been modified by genetic engineering seems to reduce the growth of superficial tumors in the bladder. But when the BCG introduced to the bladder contains DNA that gives instructions for cytokines, the tumor-fighting ability it confers on the organ is greater.

The live BCG is put inside the bladder where it causes an inflammatory response. This means that the bladder responds as though an infection were present and mounts an attack from the body's immune system. Somehow the response inhibits, or stops, tumor growth, but the way it does so is not understood.

Recommended dosage

BCG is delivered directly to the bladder via a catheter, or a tube that is inserted in the urethra. The method of delivery is called intravesical, which means it is sent directly into the cavity, or holding space, of the bladder.

The patient takes treatment once a week for six weeks and then once a month for six to twelve months. Large quantities of BCG are used. One standard dose of TheraCys calls for 81 milligrams in the first series of treatments.

Precautions

Care providers who have an immune system that is not functioning optimally should not handle BCG. Patients with HIV are at high risk for infection from BCG. All materials from BCG administration are considered biohazards.

Side effects

Most side effects fall into the category of flu-like symptoms and include chills, **fever**, and **nausea and vomiting**. There is also discomfort related to the inflammation of the bladder, particularly the feeling of an urgent need to urinate.

In a very few individuals BCG has spread throughout the body and caused infection and death. A form of pneumonia is a rare but possible side effect, and is treatable.

Interactions

Antibiotics, or drugs given to fight infection, can stop the activity of the BCG and should not be given at the same time. Chemicals that suppress the immune

KEY TERMS

Catheter—An artificial tube that is inserted in the urethra to introduce substances to the bladder, or under some circumstances, to drain the bladder.

Genetically engineered—An organism that has been modified by the intervention of humans, usually by the addition of DNA, or hereditary material, from one species to the DNA of another species.

Kilogram—Metric measure that equals 2.2 pounds.

Milligram—One-thousandth of a gram. There are one thousand grams in a kilogram. A gram is the metric measure that equals about 0.035 ounces.

Urethra—Tube that connects the bladder to the outside of the body.

system can also interfere with the action of BCG, as can **radiation therapy**.

Resources

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd., NE, Atlanta, GA 30329-4251. (800) 227-2345. <http://www.cancer.org>.

American Foundation for Urologic Disease. 300 W. Pratt St., Suite 401. Baltimore, MD 21201. Phone: (800)-828-7866.

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Barium enema

Definition

A barium enema, also known as a lower GI (gastrointestinal) exam, is a diagnostic test using x-ray examination to view the large intestine (colon and rectum). There are two types of this test: the single-contrast technique, in which barium sulfate solution is injected into the rectum to gain a profile view of the large intestine; and the double-contrast (or air contrast) technique, in which air and barium sulfate are injected into the rectum.

Purpose

A barium enema may be performed to assist in diagnosing or detecting:

- colon or **rectal cancer** (colorectal cancer)
- inflammatory diseases such as ulcerative colitis
- polyps (small benign growths in the tissue lining of the colon and rectum)
- diverticula (pouches pushing out from the colon)
- structural changes in the large intestine

The double-contrast barium enema is more accurate than the single-contrast technique for detecting small polyps or tumors, early inflammatory disease, and bleeding caused by ulcers because it gives a better view of the intestinal walls.

The decision to perform a barium enema is based on the patient's history of altered bowel habits. These alterations may include **diarrhea**, constipation, lower abdominal pain, blood, mucus or pus in the stool. It is also recommended that this exam be used every five to 10 years beginning at age 50 to screen healthy people for **colon cancer**, the second most deadly type of cancer in the United States. Those who have a close relative with colon cancer or who have had a precancerous polyp are considered to be at an increased risk for the disease and should be screened more frequently to detect abnormalities.

Precautions

Although the barium enema is an effective screening method and may lead to a timely diagnosis of a variety of gastrointestinal diseases, the test may not detect all abnormalities present in the colon and rectum. In addition, the barium enema visualizes only the large intestine; the small intestine may also require examination with an **upper GI series** to rule out abnormalities in that area of the digestive tract. Another drawback is that intestinal gas may hinder the accuracy of test results.

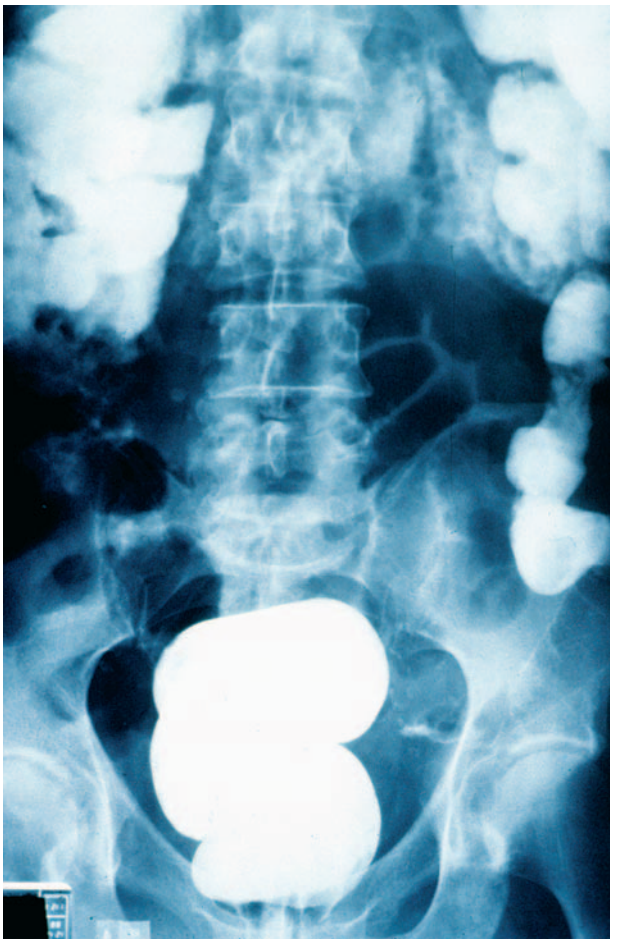
Numerous studies have shown that a **colonoscopy** performed by an experienced gastroenterologist is a more accurate initial diagnostic tool for detecting early signs of colorectal cancer than a barium enema. Colonoscopy allows a physician to examine the entire colon and rectum for polyps. In addition, if abnormalities such as polyps are observed during the procedure, these often-precancerous growths may be removed during the procedure and later examined (**biopsy**). However, a colonoscopy almost always involves conscious sedation, while the barium enema is an unsedated procedure.

Some physicians use flexible **sigmoidoscopy** (proctosigmoidoscopy) plus a barium enema instead of colonoscopy. However, sigmoidoscopy only visualizes the rectum and the portion of the colon immediately above it (sigmoid colon) and does not allow the physician to remove polyps but only to obtain tissue or stool samples. In 2003, debate continued on the use of virtual colonoscopy to replace colonoscopy and perhaps barium enema for colon and rectal cancer screening. Virtual colonoscopy refers to the use of imaging, usually with computed tomography (CT) scans or magnetic resonance imaging (MRI) to produce images of the colon. Studies in late 2003 showed that virtual colonoscopy was as effective as colonoscopy for screening purposes and it offered the advantage of being less invasive and less risky. However, many physicians were unwilling to accept it as a replacement for colonoscopy, particularly since some patients might still require the regular colonoscopy as a follow-up to the virtual procedure if a polyp or abnormality is found that requires biopsy. Studies have shown virtual colonoscopy uses less radiation that barium enema and may be more beneficial for use in children in particular. As of late 2003, the American Cancer Society still recommended a barium enema examination every five years as part of regular colon cancer screening for people over age 50.

Description

To begin a barium enema, the patient lies flat on his or her back on a tilting radiographic table in order to have x rays of the abdomen taken. After being assisted to a different position, a well-lubricated rectal tube is inserted through the anus. This tube allows the physician or assistant to slowly administer the barium sulfate into the intestine. While this filling process is closely monitored, it is important for the patient to keep the anus tightly contracted against the rectal tube to help maintain its position and prevent the barium from leaking. This step is important because the test may be inaccurate if the barium leaks. A rectal balloon may also be inflated to help retain the barium. The table may be tilted or the patient moved to different positions to aid in the filling process.

As the barium fills the intestine, x rays of the abdomen are taken to distinguish significant findings. There are many ways to perform a barium enema. One way is that shortly after filling, the rectal tube is removed and the patient expels as much of the barium as possible. Upon completing this expulsion, an additional **x ray** is taken, and a double-contrast enema exam may follow. If this procedure is done immediately, a thin film of barium will remain in the intestine, and air is then slowly injected to expand the bowel lumen (space in the intestine). Sometimes no x rays will be taken until after the air is injected. The entire test takes about 20-30 minutes.



X ray of sigmoid colon after implementation of a barium enema. *(Custom Medical Stock Photo. Reproduced by permission.)*

Preparation

In order to conduct the most accurate barium enema test, the large intestine must be empty. Thus, patients must follow a prescribed diet and bowel preparation instructions prior to the test. This preparation commonly includes restricted intake of dairy products and a liquid diet for 24 hours prior to the test, in addition to drinking large amounts of water or clear liquids 12–24 hours before the test. Patients may also be given **laxatives** and asked to give themselves a cleansing enema.

In addition to the prescribed diet and bowel preparation prior to the test, the patient can expect the following during a barium enema:

- The patient will be well draped with a gown and secured to a tilting x-ray table.

- As the barium or air is injected into the intestine, the patient may experience cramping pains or the urge to defecate.
- The patient will be instructed to take slow, deep breaths through the mouth to ease any discomfort.

Aftercare

Patients should follow several steps immediately after undergoing a barium enema, including:

- Drinking plenty of fluids to help counteract the dehydrating effects of bowel preparation and the test.
- Taking time to rest because a barium enema and the bowel preparation taken before it can be exhausting.
- Administering a cleansing enema may help to eliminate any remaining barium. The patient may have light-colored stools for 24 to 72 hours following the exam.

Risks

Although a barium enema generally is considered a safe **screening test**, it can cause complications in certain people. For example, patients with a rapid heart rate, severe ulcerative colitis, toxic megacolon (acute dilation of the colon that may progress to rupture), or a presumed perforation in the intestine should not undergo a barium enema. Patients with a known blocked intestine, diverticulitis, or severe bloody diarrhea may be tested with caution on the advice of a physician. Also, administering a barium enema to a pregnant woman is not advisable because of radiation exposure to the fetus.

Although the barium enema may cause minor stomach or abdominal discomfort in some people, more serious complications include:

- severe cramping
- nausea and vomiting
- perforation of the colon
- water intoxication
- barium granulomas (inflamed nodules)
- allergic reactions

These complications, however, are all very rare.

Normal results

When the patient undergoes a single-contrast enema, the intestine is steadily filled with barium to differentiate the colon's markings. A normal result displays uniform filling of the colon. As the barium is expelled, the intestinal walls collapse. A normal result on the x ray after the barium is expelled shows an intestinal lining with a standard, feathery appearance and no abnormalities.

The double-contrast enema expands the intestine, which is already lined with a thin layer of barium; however, the addition of air displays a detailed image of the mucosal pattern. Varying positions taken by the patient allow the barium to collect on the dependent walls of the intestine by way of gravity.

Abnormal results

A barium enema visualizes abnormalities appearing on a series of x rays, thus aiding in the diagnosis of a variety of gastrointestinal disorders and the early signs of cancer. However, most colon cancers occur in the rectosigmoid region, or upper part of the rectum and adjoining portion of the sigmoid colon, and are better detected with flexible sigmoidoscopy or colonoscopy.

Abnormal findings on a barium enema examination may include polyps, lesions or tumors, diverticula, inflammatory disease, such as ulcerative colitis, obstructions, or hernias. Structural changes in the intestine, gastroenteritis, and the size, position, and motility of the appendix may also be apparent.

KEY TERMS

Barium sulfate—A barium compound used during a barium enema to block the passage of x rays during the exam.

Colonoscopy—An examination of the upper portion of the rectum performed with a colonoscope or elongated speculum.

Diverticula—A diverticulum of the colon is a sac or pouch in the colon walls that usually is asymptomatic (without symptoms) but may cause difficulty if it becomes inflamed.

Diverticulitis—A condition of the diverticulum of the intestinal tract, especially in the colon, in which inflammation may cause pain and distended sacs extending from the colon.

Sigmoidoscopy—A visual examination of the rectum and sigmoid colon using an instrument called a sigmoidoscope.

Ulcerative colitis—An ulceration or erosion of the mucosa (lining) of the colon.

QUESTIONS TO ASK THE DOCTOR

- How long will the test take?
- Will the test be painful?
- Is barium safe?
- Can I take my usual medications the day before the test?
- How many days will the barium be in my system?
- When will I get the test results?

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American College of Gastroenterology. 4900 B South 31st Street, Arlington, VA 22206. Phone: 703-820-7400. Health Hotline: 1-800-978-7666. <http://www. acg.gi.org>.

American College of Radiology. <http://www.acr.org>.

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Barrett's esophagus

Definition

Barrett's esophagus is pre-cancerous condition in which normal cells lining the esophagus are replaced with abnormal cells that, in some people, develop into a type of cancer of the esophagus called adenocarcinoma.

Description

The esophagus is a tube 10–13 inches (25–33 cm) long and about 1 inch (2.5 cm) wide that carries food from the mouth to the stomach. Normally, the esophagus is lined with squamous epithelial cells. These cells are similar to skin cells, and look smooth and pinkish-white.

The stomach makes acid to help digest food. A different type of cell that is resistant to acid lines the stomach. These cells look red and velvety. At the place where the esophagus meets the stomach, there is a ring of muscle called the lower esophageal sphincter (LES) muscle that normally keeps acid stomach juices from backflowing into the esophagus. When this sphincter is not working correctly, due to a hiatal hernia, medications, or loss of muscle tone, acid material enters the bottom portion of the esophagus. This backflow is called reflux. When reflux occurs frequently over an extended period of time, it is called gastroesophageal reflux disease (GERD).

Acid and digestive enzymes from the stomach irritate the cells lining the esophagus. The result is inflammation of the esophagus called esophagitis, or heartburn. When the cells lining the lower esophagus are frequently exposed to stomach juices, they erode and are replaced with abnormal cells. These new cells are more resistant to stomach acids and, while they look similar to the cells lining the stomach, they are different. Under the microscope, they appear as a pre-cancerous type of cell not normally found in the body.

These new, pre-malignant cells are called specialized columnar cells. Once specialized columnar cells appear, even if the GERD is controlled and the esophagus heals, the abnormal cells remain and are not replaced with normal cells. The presence of patches of these abnormal red cells in the esophagus is known as Barrett's esophagus. The condition is named after British surgeon Norman Barrett (1903–1979).

Cancer that develops from Barrett's esophagus is called adenocarcinoma. It is one of two types of cancer of the esophagus. This type of cancer cannot occur unless the normal cells lining the esophagus have been damaged and replaced with abnormal cells.

Heartburn is an extremely common complaint. About 10% of people in the United States, or more than 20 million Americans, experience severe or frequent symptoms. Of those people who have frequent heartburn for five years or more, 10–20% develop Barrett's esophagus. From this group, approximately 5–10% go on to develop cancer. Overall, people with Barrett's esophagus have a 30- to 125-fold higher risk of developing adenocarcinoma than the general population.

Demographics

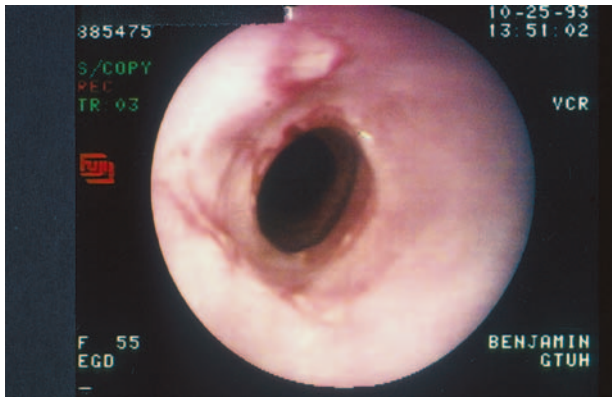
White men over age 45 who experience frequent heartburn for more than 10 years are at highest risk of developing adenocarcinoma arising from Barrett's esophagus. Adenocarcinoma is one of the most rapidly increasing types of cancer in the United States and Western Europe. Often, when the esophagus is damaged by stomach acid, the lining at the entrance to the stomach becomes thick and hard and the opening of the esophagus into the stomach narrows (stricture). People with strictures appear to be at higher risk of developing Barrett's esophagus than other people with GERD. Barrett's esophagus is rare in children.

Causes and symptoms

Barrett's esophagus is caused by gastroesophageal reflux disease that allows the stomach's contents to damage the cells lining the lower esophagus. However, every person who has GERD does not develop Barrett's esophagus. Researchers have thus far been unable to predict which people who have heartburn will develop Barrett's esophagus. While there is no relationship between the severity of heartburn and the development of Barrett's esophagus, there is a relationship between chronic heartburn and the development of Barrett's esophagus. Sometimes people with Barrett's esophagus will have no heartburn symptoms at all. In rare cases, damage to the esophagus may be caused by swallowing a corrosive substance such as lye.

The change from normal to pre-malignant cells that indicates Barrett's esophagus does not cause any particular symptoms. However, warning signs that should not be ignored include:

- frequent and long-standing heartburn
- trouble swallowing (dysphagia)
- vomiting blood
- pain under the breast bone where the esophagus meets the stomach
- unintentional **weight loss** because eating is painful



Endoscopic view of a mid-esophageal stricture in a patient with Barrett's esophagus. *(Custom Medical Stock Photo. Reproduced by permission.)*

Diagnosis

Tissue biopsies and an endoscopy are used to diagnose Barrett's esophagus. An endoscopy is normally done in a clinic under sedation or light anesthesia. A flexible fiber-optic tube is inserted through the mouth and down into the esophagus, which allows a doctor to observe the lining of the esophagus.

Sometimes the line dividing the esophagus from the stomach is not clear. Many people who have trouble with heartburn have a condition called hiatal hernia. A hiatal hernia is a stretching, or dilation, of the hole of the diaphragm that allows a bit of the stomach to bulge up into the esophagus. Because the abnormal cells that develop with Barrett's esophagus look like the cells that normally line the stomach, simply looking at the esophagus during an endoscopy is often not enough to diagnose Barrett's esophagus.

Depending on what is observed, the doctor will use tiny clips at the end of the endoscope to collect samples of tissue. This is a painless procedure. The samples are sent to the laboratory where they are examined under the microscope. Microscopic findings that abnormal cells have replaced normal cells are the only definitive diagnosis of Barrett's esophagus.

Currently, trials are underway to find alternative ways to recognize abnormal esophageal cells. One trial involves the use of laser-induced spectroscopy to visually pinpoint abnormal cells during endoscopy. This has the advantage of requiring no tissue biopsies, and allows the doctor to make an immediate diagnosis rather than wait several days for laboratory results. The technique, however, is still in the experimental stage and is not part of normal clinical practice.

Treatment team

A gastroenterologist (a specialist in diseases of the digestive system) will diagnose and monitor Barrett's esophagus. Should the pre-malignant cells of Barrett's esophagus develop into adenocarcinoma, an oncologist (cancer specialist) or a cancer surgeon will take over treatment of the cancer.

Clinical staging, treatments, and prognosis

The American College of Gastroenterologists (ACG) recognizes five stages of cellular changes in **biopsy** samples obtained from the esophagus. These are (in increasing severity):

- Negative: No abnormal changes in the cells.
- Indefinite: A few cellular changes; often difficult to distinguish from low-grade dysplasia.
- Low-grade dysplasia: Some signs of cellular abnormality are present.
- High-grade dysplasia: Many signs of cellular abnormality are present.
- Carcinoma: Malignant cells are present.

Treatment and monitoring of Barrett's depends on the results of the biopsies. First-line treatment is aimed at stopping stomach acid from entering the esophagus and giving the lining of the esophagus a chance to heal. Two categories of drugs are used to prevent the stomach from producing acid. Histamine$_2$ blockers include cimetidine (Tagamet), ranitidine (Zantac), and nizatidine (Axid). Proton pump inhibitors include omeprazole (Prilosec)and lansoprazole (Prevacid). Lifetime therapy is usually necessary to control GERD, and higher than normal doses of these drugs may be necessary for people with Barrett's esophagus. Surgery to control GERD is recommended only when these drugs are ineffective or if the patient is unwilling or unable to continue taking them.

Monitoring by endoscopy with biopsies has been the standard approach to Barrett's esophagus. However, there is some debate about the effectiveness of the monitoring in detecting **adenocarcinomas** and about how cost-effective the monitoring is. Research in this area continues, but ACG guidelines (1999) suggest the following monitoring program:

- Negative or indefinite biopsies: At least two follow-up endoscopies and biopsies at two- to three-year intervals.
- Low-grade dysplasia: Endoscopies and biopsies every six months for a year, then every year if low-grade dysplasia continues.

KEY TERMS

Diaphragm—The muscle that separates the abdominal cavity (stomach and intestines) from the thoracic cavity (heart and lungs).

Dysplasia—The abnormal change in size, shape, or organization of adult cells.

Treatment of high-grade dysplasia is controversial. Diagnosis of high-grade dysplasia requires confirmation by at least one expert pathologist, with two experts' opinions recommended. One treatment choice is surgery to remove the esophagus (esophagectomy). About 40–45% of people who have high-grade dysplasia also have previously undetected adenocarcinoma. The advantage of surgically removing the esophagus is that the cancerous cells are also removed. However, in 2004 physicians emphasized that acid suppression is definitely favored over surgery, as is a new form of surgery called duodenal diversion.

The alternative to surgery is to continue to monitor cellular changes with endoscopies and biopsies every three months. The choice of treatment depends both on the health of the patient and on the patient's preference.

Surgical removal of the esophagus is the only effective way known to treat adenocarcinoma. The survival rate for people who progress from Barrett's esophagus to adenocarcinoma is poor, with fewer than 10% surviving five years. However, the earlier the cancer is detected and the esophagus removed, the greater the chances of survival.

Alternative and complementary therapies

Several non-medical ways to prevent GERD can be used effectively along with drug treatments that block the production of stomach acid. These include:

- raising the head of the bed a few inches on bricks to encourage gravity to keep the stomach contents from rising into the esophagus
- eliminating caffeine, acidic foods such as orange juice, and spicy foods from the diet
- eating smaller, more frequent meals, rather than large meals
- not eating within three hours of going to bed None of these methods have any reported adverse side effects.

Clinical trials

Since adenocarcinoma arising from Barrett's esophagus is one of the fastest-growing cancers in the United

QUESTIONS TO ASK THE DOCTOR

- How would you characterize the changes in the cells in my esophagus?
- What kind of drugs will you prescribe to control my reflux?
- What frequency of endoscopic monitoring do you propose?
- What are the chances of my Barrett's esophagus progressing to adenocarcinoma?
- If high-grade dysplasia is present, where can I get a second opinion?
- If high-grade dysplasia is present, what is involved in a esophagectomy?
- What is daily life like after an esophagectomy?
- Where can I find out more about clinical trials using drugs and light from a laser (called endoscopic laser photablation) to treat adenocarcinoma?
- What changes in my lifestyle can I make to help control my reflux?
- If my GERD cannot be controlled with medication, what is involved in surgery to control reflux?
- Are there any particular signs or symptoms that suggest that I should see a doctor immediately rather than waiting until my next scheduled endoscopy?

States and Europe, it has sparked new research activity concerning more sensitive ways to identify high-grade dysplasia, the best methods of monitoring Barrett's esophagus, and the techniques to remove adenocarcinoma without removing the entire esophagus. One of these **clinical trials** involves using drugs to make cancer cells more sensitive to light, and then using a laser to kill these cells in the esophagus. Another clinical trial involves determining if genetic markers can be used to predict which people with Barrett's esophagus are at risk for developing cancer.

The selection of clinical trials underway changes frequently. Current information on clinical trials in process and where they are being held is available by entering the search term "Barrett's esophagus" at the following Web sites:

- National Cancer Institute <http://cancertrials.nci.nih.gov> or 1-800-4-CANCER.
- National Institutes of Health Clinical Trials <http://clinicaltrials.gov>.
- Center Watch: A Clinical Trials Listing <http://www.centerwatch.com>.

Prevention

People cannot get esophageal adenocarcinoma unless the cells lining the esophagus are damaged. Prevention, therefore, involves prompt treatment of GERD. Some studies have found that factors that increase the risk of a person with the Barrett's esophagus condition developing into adenocarcinoma include heavy smoking, being overweight, and a family history of gastric cancer. People with chronic gastroesophageal reflux symptoms, particularly those over age 50, should have a screening upper endoscopy.

Special concerns

People who are diagnosed with Barrett's esophagus should expect to eliminate caffeine from their diet as caffeine stimulates the production of stomach acid. Other foods that may need to be eliminated include citrus fruits and juices, tomatoes, and spicy foods.

People with high-grade dysplasia are faced with the stressful decision of whether to undergo surgical removal of the esophagus and endure the lifestyle changes that loss of the esophagus involves, or whether to proceed with intensive monitoring, realizing that monitoring is not totally effective and that cancer may not always be detected early. People faced with this decision should discuss the matter with their physicians, their loved ones, and support group members to get a balanced picture of how their lives may be changed by their choices.

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Basal cell carcinoma

Definition

A basal cell carcinoma is a skin cancer that originates from basal keratinocytes in the top layer of the skin, the epidermis. Sometimes these tumors are called "rodent ulcers."

Description

Basal keratinocytes are unpigmented skin cells found deep in the epidermis, hair follicles, and sweat glands. When they become cancerous, these cells invade the dermis (the layer of skin just below the epidermis) and spread out into the normal skin. They become visible as a small growth or area of change in the skin's appearance. These tumors can appear anywhere on the body, but most become evident on the face and neck.

Most basal cell carcinomas are small tumors that can be cured with simple surgeries. They usually grow quite slowly. However, neglected or aggressive tumors can invade vast amounts of skin. These cancers can also spread along bones, cartilage, muscles, and, more rarely, nerves. Some tumors may eventually reach the eye or brain or become large enough to significantly disfigure the face. These serious consequences are more likely if the tumor lies close to bone and cartilage—for instance, at the corner of the eye. Very few basal cell carcinomas spread to more distant organs; no more than five out of every 10,000 of these tumors metastasize. Most that do are very large, deep cancers that have been visible for years.

Demographics

Basal cell carcinomas are most common from middle age until old age. They are more frequent in men than women. These cancers seem to be associated with exposure to ultraviolet light; they tend to develop on sun-exposed areas and are more common in people living near the equator. Those who have lighter skin are more susceptible; fair-haired blonds are more likely to develop tumors than people with darker complexions. In the United States, Caucasians have a 28% to 33% chance of developing a basal cell carcinoma over a lifetime.

Weakened immunity may also play a role. Those who have had an organ transplanted or who have contracted acquired immune deficiency syndrome (AIDS) are more likely to develop one of these cancers.

Basal cell carcinomas are particularly common among individuals with a rare genetic disease called nevoid basal cell carcinoma syndrome (Gorlin's syndrome). Individuals with this disease can be born with basal cell carcinomas or begin to develop them in childhood. Some have few or no cancers; others have more than 250. These tumors seldom grow much before puberty, but during and after adolescence they can spread rapidly. Other symptoms include small pits in the palms and soles, cysts in the jaw, and other abnormalities in the bones.

Causes and symptoms

Basal cell carcinomas are caused by genetic damage to a skin cell. Exposure to ultraviolet light and x rays, suppression of the immune system, and genetic factors seem to increase the risk that this will happen. The exact cause, however, is rarely known.

Several types of basal cell carcinomas exist. Nodular basal cell carcinomas are the most common form. These tumors begin as a tiny red or clear bump on the skin. Over time, they develop into a growth with clear or white "pearly" raised edges and, often, a depressed area in the middle. A network of tiny blood vessels usually crisscrosses the surface, and the tumor may bleed repeatedly or crust over. Morpheaform (sclerosing, morpheic) basal cell carcinomas are more difficult to detect. These tumors are usually pale, firm, flat growths that can blend into the normal skin around them. Many look just like a scar. Superficial basal cell carcinomas are flat, red, scaly plaques that can look like psoriasis or eczema. Unlike other basal cell carcinomas, they are usually found on the arms, legs, and torso. Pigmented basal cell carcinomas are brown, black, or blue; they are usually of the nodular type and can look like a **melanoma**.

Some general characteristics of skin cancers include:

- irregular or ragged borders
- non-symmetrical shape
- a change in color
- a size greater than 0.2 inches (6 mm)

Diagnosis

Basal cell carcinomas are usually diagnosed with a skin **biopsy** taken in the doctor's office. This is generally a brief and simple procedure. After numbing the skin with an injection of local anesthetic, the doctor snips out a tiny piece of the tumor. The skin sample must be sent to a trained pathologist to be analyzed. It may take up to a week for the biopsy results to come back. Sometimes the tumor is removed immediately after the biopsy, before the results are known.

Treatment team

Primary care physicians remove some basal cell carcinomas; other cancers, including larger or more complicated tumors, may be referred to a dermatologist. The services of a plastic surgeon are occasionally necessary. In the rare event that a tumor metastasizes, an oncologist and full cancer treatment team become involved.

Clinical staging, treatments, and prognosis

Basal cell carcinomas rarely spread into the lymph nodes and internal organs. For this reason, doctors tend not to stage them. If staging is needed, the TNM (tumor, lymph node, and metastases) system is usually used. For basal cell carcinomas, this can be simplified into the following five categories:

- Stage 0: The cancer is very small and has not yet spread from the epidermis to the dermis.
- Stage 1: The cancer is less than 2 cm (0.8 inches) in diameter. No cancer cells can be found in lymph nodes or other internal organs.
- Stage 2: The cancer is more than 2 cm (0.8 inches) in diameter. No cancer cells can be found in lymph nodes or other internal organs.
- Stage 3: Cancer cells have been found either in nearby lymph nodes or in the bone, muscle, or cartilage beneath the skin (or in both locations).
- Stage 4: Cancer cells have been discovered in internal organs, most often the lungs or lymph nodes, that are distant from the skin. A stage four cancer can be any size.

Treatment options for non-metastatic, non-staged tumors

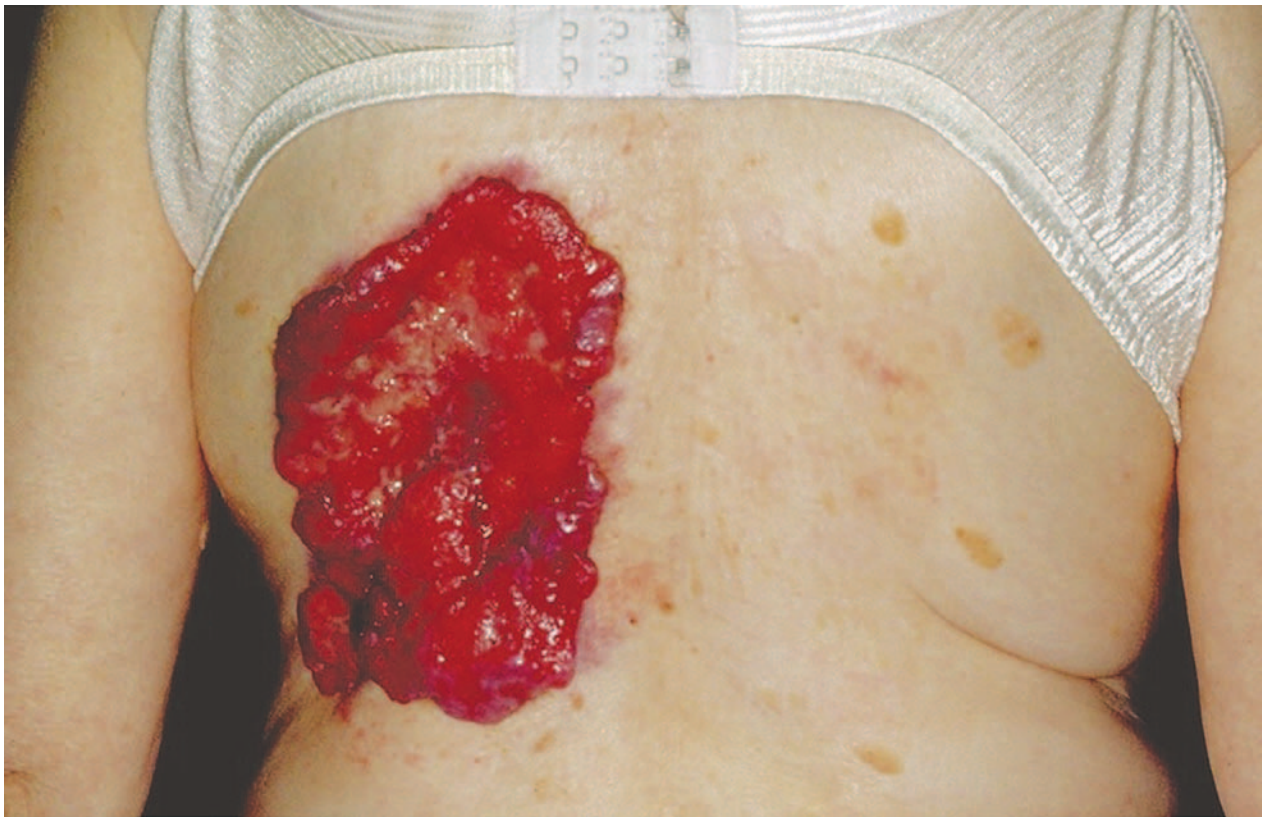
For most non-metastatic, non-staged cancers, there may be several treatment options. The recommended treatment depends on the size and type of tumor, its location, and cosmetic considerations. The cure rates for most of the following techniques are approximately 85% to 95%, but vary with tumor size and other factors. Moh's micrographic surgery has a five-year cure rate of 96%. Success rates for recurrent tumors are approximately 50% with most techniques and 90% with **Moh's surgery**.

In conventional surgery, the doctor numbs the area with an injection of local anesthetic, then cuts out the tumor and a small margin of normal skin around it. The wound is closed with a few stitches. One advantage to conventional surgery is that the wound usually heals quickly. Another benefit is that the complete cancer can be sent to a pathologist for evaluation. If the skin around the tumor is not completely free of cancer cells, the tumor can be treated again immediately.

Moh's micrographic surgery is a variation of conventional surgery. In this procedure, the surgeon examines each piece of skin under the microscope as it is removed. If any cancer cells remain, another slice is taken from that area and checked. These steps are repeated until the edges of the wound are clear of tumor cells, then the wound is closed. The advantage to this technique is that all of the visible cancer cells are removed but as much normal skin as possible is spared. Moh's surgery is often used for larger or higher risk tumors and when cosmetic considerations are important. The main disadvantage is that it takes much longer than conventional surgery and requires a specially trained surgeon.

A laser is sometimes used as a cutting instrument instead of a scalpel. Laser light can also destroy some cancer cells directly. A disadvantage to laser surgery is that the wounds from some lasers heal more slowly than cuts from a scalpel. The advantage is that bleeding is minimal.

In electrodessication and curettage, the physician scoops out the cancer cells with a spoon-shaped instrument called a curette. After most of the tumor is gone, the remaining cancerous tissue is destroyed with heat from an electrical current. The wound is left open to heal like an abrasion. It leaks fluid, crusts over, and heals during the next two to six weeks. This is a safe and easy method for removing many basal cell carcinomas. One disadvantage is that there is no skin sample to confirm that the tumor is completely gone. The electrical current used during this surgery can interfere with some pace-



A basal cell carcinoma tumor. *(Custom Medical Stock Photo. Reproduced by permission.)*

makers and larger tumors may heal with a noticeable scar.

In cryosurgery, liquid nitrogen is used to freeze the tumor and destroy it. This treatment is another type of blind destruction; there is no skin sample to make sure the cancer cells have all been killed. Patients report swelling and pain after cryosurgery, and a wound appears a few days later where the cells were destroyed. When the site heals, it has usually lost its normal pigment. There is a risk of nerve damage with this technique.

Radiation therapy is an uncommon treatment for basal cell carcinoma. One disadvantage is the inconvenience: multiple treatments, over a period of weeks, are necessary. Tumors that return after radiation also tend to grow more quickly than the original cancer. In addition, x rays may promote new skin cancers. Radiation therapy may be an option for patients who cannot undergo even minor surgery. It is also used occasionally as an adjunct to surgery. One advantage is that the cosmetic results can be very good.

Occasionally a lotion containing **fluorouracil** is applied to the tumor. This drug cannot penetrate very far and cancer cells in the deeper parts of the tumor may not be destroyed. The main advantage to this treatment is its simplicity.

Treatment options for metastatic cancers

Cancers that have spread to internal organs are treated with a combination of surgery, radiation, and **chemotherapy**.

Prognosis

The prognosis for small, uncomplicated basal cell carcinomas is very good. The vast majority of these tumors can be successfully removed. However, cancers that were not completely destroyed may regrow. If the edges of the removed skin contain cancer cells, the chance that the tumor will return within the next five years is about 40%. Regrowth is more likely with cancers larger than 0.8 inches (2 cm), those on the face (particularly around the nose, eye, and ear), and higher risk types such as morpheaform tumors. Tumors can redevelop in the scar from the surgery, on the edges of the surgery site, or deep in the skin. These cancers may not look like the original tumor. Patients should be particularly watch-

ful for minor changes in the appearance of the scar or sores that appear nearby.

Cancers that metastasize spread most often to the lymph nodes and lungs. The prognosis for metastatic cancers is poor, even with treatment. Survival after spread of the cancer to internal organs is eight months on the average and seldom more than a year and a half.

Coping with cancer treatment

Most basal cell carcinomas are removed with techniques that cause few, if any, lasting side effects. Patients who have cosmetic concerns may wish to discuss them with their doctor.

Clinical trials

In photodynamic laser therapy, a dye activated by laser light destroys the cancer. This dye is spread onto the skin, injected, or drunk. During a waiting period, normal cells clear the dye, then a laser activates the remainder. As of 2001, this technique was only useful for cancers very near the surface of the skin. One side effect after treatment is a period of excessive sun-sensitivity. Several **clinical trials** are in progress.

In 1999, researchers first reported that imiquimod 5% cream, spread onto the skin several times a week, could destroy small nodular or superficial basal cell carcinomas. The side effects from this treatment were mainly local skin reactions such as **itching**, rashes, and redness. In 2003, new studies continued to show its effectiveness and the drug company that marketed the cream filed new applications with the U.S. Food and Drug Administration (FDA) for treatment of superficial basal cell carcinoma.

Interferon alpha injected into the tumor is sometimes effective for basal cell carcinomas. This experimental treatment is mainly used for less dangerous forms such as the nodular type.

Retinoids, drugs related to vitamin A, may have some effect on basal cell carcinomas. These drugs are taken internally and can have significant serious side effects.

Prevention

The risk factors for basal cell carcinoma include:

- ethnic background
- complexion
- geographic location
- increasing age

KEY TERMS

Albinism—A genetic disease characterized by the absence of the normal skin pigment, melanin.

Biopsy—A sample of an organ taken to look for abnormalities. Also, the technique used to take such samples.

Dermis—A layer of skin sandwiched between the epidermis and the fat under the skin. It contains the blood vessels, nerves, sweat glands, and hair follicles.

Epidermis—The thin layer of skin cells at the surface of the skin.

Fluorouracil—A cancer drug.

Hair follicles—The structures in the skin that make each hair.

Imiquimod—A drug, approved by the FDA to treat warts, that may destroy basal cell carcinomas by stimulating the immune system. Also known by its trade name Aldara.

Interferon alpha—A chemical made naturally by the immune system and also manufactured as a drug.

Local anesthetic—A liquid used to numb a small area of the skin.

Lymph node—A small structure located throughout the body (part of the lymphatic system) designed to filter the flow of lymph, a usually clear fluid that originates from stem cells.

Nonsteroidal anti-inflammatory drugs (NSAIDS)—A class of drugs that suppresses inflammation. Includes a wide variety of drugs, such as aspirin.

Oncologist—A doctor who specializes in the treatment of cancer.

Pathologist—A doctor who specializes in examining cells and other parts of the body for abnormalities.

Premalignant skin lesion—An abnormal change in the skin that has a good chance of turning into skin cancer but is not yet cancerous.

Selenium—A mineral needed in extremely small quantities by the body. Large amounts can be very toxic.

Squamous cell carcinoma—A type of skin cancer.

Sweat glands—Tiny glands scattered throughout the skin that produce sweat.

TNM system—A commonly used staging system that examines the main tumor (T), the lymph nodes (N), and metastases (M).

Xeroderma pigmentosum—A genetic disease characterized by the inability to repair damaged DNA. Individuals with this disease develop an excessive number of skin cancers.

QUESTIONS TO ASK THE DOCTOR

- What treatment(s) would you recommend for my tumor?
- How effective would you expect each of them to be, for a tumor of this size and in this location?
- How much cosmetic damage am I likely to see with each treatment?
- Are there any alternatives?
- How should I prepare for the procedure?
- What is the risk that my tumor in particular will regrow?

- exposure to x rays and ultraviolet light (both UVA and UVB)
- a history of premalignant skin lesions or skin cancer
- genetic disorders such as nevoid basal cell carcinoma syndrome, xeroderma pigmentosum, and albinism
- suppression of the immune system by AIDS or an organ transplant

Some important preventive steps include wearing protective clothing and hats in the sun, using a sunscreen, avoiding the sun between 10 A.M. and 4 P.M., and staying away from suntanning booths. Checking the skin for early signs of cancer also is critical.

Drugs related to vitamin A (including beta-carotene, retinol, and isotretinoin), vitamin E, nonsteroidal anti-inflammatory drugs (NSAIDS), and selenium have been suggested as possibly preventing basal cell carcinoma. A 2003 study reported that selenium is not effective in preventing basal cell carcinoma and may even increase risk of squamous cell carcinoma.

Special concerns

Because many basal cell carcinomas are found on the face and neck, cosmetic concerns are a priority for many patients. If there is a risk of noticeable scarring or damage, a patient may wish to ask about alternative types of removal or inquire about the services of a plastic surgeon.

After treatment, it is important to return to the doctor periodically to check for regrowth or new skin cancers. Approximately 36% of all patients find a new basal cell or squamous cell carcinoma within the next five years. Having a basal cell carcinoma before the age of 60 may also increase the chance of developing other cancers in internal organs.

See also Chemoprevention; Familial cancer syndromes; Reconstructive surgery.

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BCG *see* **Bacillus Calmette Guerin**

Benzodiazepines

Definition

Benzodiazepines are a family of tranquilizers used to treated anxiety and insomnia. In cancer patients, it is used primarily to treat nausea resulting from **chemotherapy**.

Purpose

Everyone at times feels nervous or anxious. Usually, the feeling is related to something happening in the person's life, such as an upcoming job interview or a speech to a large audience, and it goes away when life returns to normal. This type of anxiety does not need medical treatment. But some people feel anxious almost all the time, or they respond to slightly stressful events with feelings that are out of proportion to the actual situation. The constant anxiety, irrational worries, and sense of impending doom can seriously interfere with their daily lives. For people with such intense or prolonged anxiety, benzodiazepines can help bring their feelings under control and reduce symptoms such as rapid heartbeat, breathing problems, irritability, nausea, and faintness. Benzodiazepines are prescribed for severe general anxiety and for specific anxiety disorders, such as phobias, panic disorder, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder. Physicians may sometimes prescribe these drugs for other conditions, such as sleep disorders, epilepsy, and other seizure disorders. In cancer patients, they are sometimes used to treat people who are overly anxious about their condition, but more commonly, they are prescribed to treat nausea associated with **radiation therapy** and chemotherapy.

Description

Benzodiazepines have a large number of uses, including treatment of panic attacks, treatment of anxiety, short-term treatment of insomnia, control of the symptoms of alcohol withdrawal, including hallucinations, and as skeletal muscle relaxants. In cancer therapy, they are used in combination with other drugs for control of **nausea and vomiting**. In both cancer and surgery, the benzodiazepines may be used to impair memory of unpleasant experiences. This may be particularly useful in some types of cancer therapy where the adverse effects of the treatment may be so severe that patients resist returning for additional courses of therapy. One benzodiazepine (Midazolam) has been useful in induction of anesthesia prior to surgery.

Benzodiazepines, and drugs which are similar to benzodiazepines, have been widely used as sedatives because they are relatively non-toxic. Unlike barbiturates, which were commonly used as sleeping pills, overdoses of the benzodiazepines are almost never fatal.

unfortunately, benzodiazepines are addictive, and so efforts must be made to limit their use whenever possible.

The most common causes of nausea and vomiting in cancer patients include treatment with chemotherapy and radiation therapy; tumor spread to the gastrointestinal tract, liver, and brain; constipation; infection; and use of some opioid drugs used to treat cancer pain. The mechanisms that control nausea and vomiting are not fully understood, but both are controlled by the central nervous system. The prevention and control of nausea and vomiting are extremely important for patients receiving cancer treatment, particularly chemotherapy (the treatment of cancer with strong chemical agents).

Unrelieved nausea and vomiting may lead to nutritional deficiencies, dehydration, electrolyte imbalances, and a general deterioration of the patient's mental and physical status. The drugs used to treat nausea and vomiting are known as **antiemetics**. Benzodiazepines are valuable tools in the prevention and treatment of nausea and vomiting when given in combination with other antiemetics. They are especially useful in preventing anticipatory nausea and vomiting.

When nausea and vomiting result from chemotherapy administration, the nausea and vomiting can be classified as anticipatory, acute, or delayed. Anticipatory nausea and vomiting occur prior to the actual chemotherapy treatment and is a response primarily to an environmental stimulus, such as a specific odor, which is then associated with the chemotherapy treatment in the future. Acute nausea and vomiting occur within 24 hours of administration of the chemotherapeutic agent. Delayed

nausea and vomiting occur after the acute phase and may last 48 or more hours after chemotherapy administration.

Benzodiazepines may be used in conjunction with antiemetics in the prevention and treatment of anxiety and anticipatory chemotherapy-induced nausea and vomiting. These agents appear to be especially effective in therapy regimens that have a high risk of causing vomiting when given to children. The benzodiazepines have only modest antiemetic properties. Therefore, they are usually used as adjuncts to antiemetic agents.

The family of antianxiety drugs known as benzodiazepines includes alprazolam (Xanax), chlordiazepoxide (Librium), clonazepam (Clonipin), diazepam (Valium), and **lorazepam** (Ativan). Benzodiazepines take effect fairly quickly, starting to work within an hour after they are taken. Note that there may be considerable variation between individuals in metabolism of benzodiazepines, so patient response may not be predictable.

As of 2005, there are 13 benzodiazepines in use in the United States, but additional drugs of this type are used in other nations. Although most of these drugs have similar properties, they may be used for different purposes depending on their onset and duration of action.

- Alprazolam (Xanax) is an intermediate acting drug, used both for treatment of anxiety and for panic attacks. Alprazolam has been useful in controlling anxiety that stems from **depression**.
- Chlordiazepoxide (Librium) is an intermediate acting benzodiazepine which has been used for short-term treatment of anxiety, control of alcohol withdrawal, and control of the anxiety that precedes surgery.
- Clonazepam (Klonopin) has an intermediate onset and relatively long duration of action. It is used to control panic attacks, but most often is used in treatment of seizure disorders. For this purpose, it has been useful in control of some types of seizures that have resisted other types of anti-epileptic medications.
- Clorazepate (Tranxene) is used to treat anxiety disorders, for treatment of alcohol withdrawal, and in combination with other drugs for the treatment of partial seizures.
- Diazepam (Valium) is used to control anxiety, for control of the symptoms of alcohol withdrawal, for relief of the anxiety seen prior to surgical procedures, and as a muscle relaxant. For this purpose it is used to control muscle spasms and as part of the treatment of tetanus. As an anti-convulsant, diazepm is used to treat severe seizures including status epilepticus. Because diazepam, like other drugs in this class, can impair short-term memory, it is sometimes administered after some medical procedures to blur the effects of an unpleasant experience.
- Estazolam (Pro Som) is used as a sedative in short-term treatment of insomnia.
- Flurazepam (Dalmane) is used as a sedative for short-term treatment of insomnia.
- Lorazepam (Ativan) is used to treat anxiety, including the anxiety associated with depression, for control of resistant seizures, including status epilepticus, and relax surgical patients before administration of anesthesia.
- Midazolam (Versed) is used to relax surgical patients before administration of anesthesia, and, for short surgical or diagnostic procedures, it may be the sole source of anesthesia. The Midazolam package insert has an important warning regarding its use: *Midazolam IV has been associated with respiratory depression and respiratory arrest. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy resulted. Use Midazolam IV only in hospital or ambulatory care settings, including physicians' offices that provide for continuous monitoring of respiratory and cardiac function. Assure immediate availability of resuscitative drugs and equipment and personnel trained in their use.*
- Oxazepam (Serax) is approved for treatment of anxiety disorders and the short-term treatment of anxiety, including anxiety associated with depression. Oxazepam is approved for control of symptoms of alcohol withdrawal and control of anxiety, tension, agitation, and irritability in the elderly.
- Quazepam (Doral) is used for short-term treatment of insomnia.
- Temazepam (Restoril) is used for short-term treatment of insomnia.
- Triazolam (Halcion) is used for the short-term treatment of insomnia.

Although not officially approved for this use, several of the benzodiazepines (chlordiazepoxide, diazepam, clorazepate, lorazepam, oxazepam, and alprazolam) have been used, with some success, in control of irritable bowel syndrome. Alprazolam has been studied for use in treatment of premenstrual syndrome.

Recommended dosage

Benzodiazepine dosage should be individualized to minimize sedation. The normal dose of alprazolam is 0.25–0.5 mg. The usual dose of lorazepamis 2–3 mg. The normal dosage of clonazepam is 0.5–2 mg. The usual dosage range of temazepam (Restoril) is 15–30 mg. Doses may be repeated if necessary.

There can be great differences from person to person in the length of time it takes to remove benzodiazepines

from the body. For example, the half-life of diazepam, the length of time it takes to remove half of a single dose of the drug, can range from 20 to 80 hours. In addition, it has an active metabolite, desmethyldiazepam, which has a half-life that ranges from 30 to 200 hours. These differences may be even greater in the elderly. Some benzodiazepines, such as alprazolam, clonazepam, lorazepam, and triazolam, do not have active metabolites, and so their duration of action is easier to predict. Even so, the half lives of these drugs may vary by 100% from one person to the next. Because elderly people normally metabolize drugs at a slower rate than younger patients, careful monitoring and dose adjustments are essential.

Precautions

Prolonged use of benzodiazepines in therapeutic doses can lead to dependence. Withdrawal syndrome has occurred after as little as 4 to 6 weeks treatment. It is more likely if the drug is short acting, taken regularly for over three months and abruptly discontinued. It was once believed that benzodiazepines with a long duration of action, or long lasting metabolites, could not cause withdrawal symptoms because the slow elimination of the drug would act as a form of dose adjustment. This is not true, and all benzodiazepines that have been used for a month or longer should be discontinued by slowly lowering the dose.

Benzodiazepines should not be used in patients with psychosis, acute narrow angle glaucoma, or liver disease. The drugs can act as respiratory depressants and should be avoided in patients with respiratory conditions. Benzodiazepines are potentially addictive and should not be administered to patients with **substance abuse** disorders. Because benzodiazepines are sedatives, they should be avoided in patients who must remain alert. Their use for periods over four months has not been documented. These drugs should not be used during the second and third trimester of pregnancy, although use during the first trimester appears to be safe. They should not be taken by women who are breastfeeding their babies. Parents should consult specialized references for use in children.

Benzodiazepines have long been known to pose serious risks to older people that include impaired thinking, unsteady gait, dizziness, and increased risk of hip fracture. Most of these drugs are cleared from the body more slowly in older adults, thus leading to dangerous accumulation with repeated use.

Patients should never stop taking a benzodiazepine abruptly. Doing so can lead to withdrawal symptoms such as convulsions, tremor, abdominal and muscle cramps, vomiting, and sweating. When it is time to discontinue the medication, the doctor will probably reduce the dosage gradually to avoid withdrawal symptoms. Patients who follow their prescribed medication schedules carefully should have no problems. However, sometimes a patient accidentally takes too much medication, which can result in continuing confusion, severe drowsiness, shakiness, slurred speech, staggering, unusually slow heartbeat, and severe weakness. Anyone experiencing these reactions should seek medical help at once.

When used in patients in whom several different types of seizure disorders coexist, clonazepam may increase the incidence or precipitate the onset of generalized tonic-clonic (grand mal) seizures. This may require the addition of other anticonvulsants or an increase in their dosage.

Side effects

Benzodiazepines are effective in the treatment of anxiety and nausea in cancer patients yet is controversial because of their dependency potential. Benzodiazepines work quickly and have usually few serious side effects. An increased risk of falls and memory impairment, particularly in the elderly, have been noted. Tolerance to their sedative effects develops, but not to their antianxiety properties.

The most common side effects of benzodiazepines include sedation and sleepiness. More rare side effects are:

- depression
- lethargy
- apathy
- fatigue
- hypoactivity
- lightheadedness
- memory impairment
- disorientation
- anterograde amnesia
- restlessness
- confusion
- crying or sobbing
- delirium
- headache
- slurred speech
- aphonia (loss of voice)
- dysarthria
- stupor

- seizures
- coma
- fainting
- rigidity
- tremor
- dystonia
- dizziness
- euphoria
- nervousness
- irritability
- difficulty in concentration
- agitation
- inability to perform complex mental functions
- uncontrollable limb and body movements
- unsteadiness
- lack of coordination
- weakness
- vivid dreams
- psychomotor (bodily movement triggered by mental activity, especially voluntary muscle action)
- retardation
- "glassy-eyed" appearance
- paradoxical reactions such as over-excitability, hallucinations, insomnia, and rage

Other reactions include changes in heart rate and blood pressure, changes in bowel function, severe skin rash and changes affecting the genital and urinary organ functions. Other adverse effects have been reported.

Interactions

The sedating effect of these drugs also can be greatly increased if taken with other drugs that are central nervous system (CNS) depressants, such as antihistamines or other medicines for allergies or colds, sedatives, sleeping medicine, and prescription pain relievers, including narcotics. The metabolism of alprazolam may be increased by: cimetidine, oral contraceptives, disulfiram, fluoxetine, isoniazid, ketoconazole, metoprolol, propoxyphene, propranolol, and valproic acid. The absorption of all benzodiazepines is inhibited by concomitant use of antacids. Benzodiazepines may increase blood levels of digoxin, and reduce the efficacy of levodopa. Other drug interactions have been reported.

It is particularly important to avoid alcohol when taking a benzodiazepine. Alcohol is a powerful central nervous system depressant. Combining large amounts of these two substances can lead to unconsciousness and even death. Use of the ulcer drug cimetidine (Tagamet) along with diazepam or chlordiazepoxide may slow down the metabolism of the anti-anxiety drugs, thus keeping them in the bloodstream longer and prolonging their effects.

Ken R. Wells

KEY TERMS

Antiemetics—Medications that prevent vomiting.

Aphonia—Loss of voice.

Chemotherapy—The use of chemicals to treat diseases, especially cancer.

Glaucoma—An eye disorder marked by abnormally high pressure within the eyeball.

Opioid—Any of various opium-containing substances that are produced naturally in the brain.

Psychosis—A loss of contact with reality.

Bevacizumab

Definition

Bevacizumab is an antibody produced in a laboratory that is used to reduce the size of tumors in corectal cancer that has metastasized. It is also being used experimentally to treat other metastic cancers.

Purpose

Bevacizumab is used as a first-line treatment for advanced cancer of the colon or rectum that has metastasized or spread to other parts of the body. It is used in combination with intravenous **chemotherapy** that consists of a combination of **irinotecan**, 5-fluorouracil and **leucovorin**. This is known as IFL chemotherapy.

Corectal cancer affects the colon, or large intestine and the rectum, which is the terminal portion of the large intestine. It is the second leading cause of cancer death in the United States and accounts for about 15% of all new cancers that are diagnosed each year.

Description

Bevacizumab is an antibody made partially of a mouse (murine) protein that comes from Chinese hamster ovary cells. It sold in the United States under the

brand name Avastin and is manufactured by Genentech. It was approved for use by the United States Food and Drug Administration (FDA) in February 2004. Generic substitutes are not available.

Bevacizumab works by blocking the action of a protein called vascular endothelial growth factor (VEGF). VEGF stimulates the growth of new blood vessels, a process called angiogenesis. The antibodies in bevacizumab are designed to bind tightly to VEGF. This inactivates VEGF so that it is no longer an effective stimulant. As a result, new blood vessels are not formed. Cancer tumors depend on the development of new blood vessels to grow. Without an adequate supply of blood, they cannot get larger and may even shrink. Bevacizumab does not work directly on the tumor, but prevents its growth by reducing its supply of blood.

Bevacizumab does not cure corectal cancer, but it can slow its growth and increase survival times. It is normally given immediately after treatment with ILF chemotherapy. Bevacizumab is thought to have great promise in slowing the growth of inoperable tumors. As of 2005, it was being tested in more than three dozen **clinical trials** in combination with other drugs to treat many other types of metastic cancer including **non-small cell lung cancer**, pancreatic cancer, head and neck tumors, **ovarian cancer**, malignant **melanoma**, and solid tumors in children and adults. Information on current clinical trials that are enrolling patients can be found at <http://www.clinicaltrials.gov>.

Recommended dosage

Bevacizumab is a liquid that will be diluted by the physician before use. The dose given is based on body weight and is administered every 14 days. Bevacizumab is given intravenously (IV). The first dose is dripped into a vein over 90 minutes following chemotherapy. If this dose is well tolerated and no infusion reactions occur, the second dose is infused over 60 minutes and subsequent doses are administered over a period of 30 minutes.

Precautions

Bevacizumab may cause birth defects in a developing fetus. It should not be used by women who are pregnant, breastfeeding, or trying to become pregnant. It should not be used by men who are attempting to conceive a child. Both men and women who are sexually active should use contraception while receiving bevacizumab therapy.

Bevacizumab should not be started until 28 days after major surgery and after incisions are completely healed, because it slows or prevents wound healing. It should be stopped at least 28 days before elective surgery, because it takes an average of 20 days to be cleared from the body.

KEY TERMS

Angiogenesis—The process the body uses to develop new blood vessels.

Antibody—A substance produced by the immune system to fight disease.

Colon—A part of the digestive system, specifically the first six feet of the large intestine.

Rectum—The last 8–10 inches of the large intestine ending in the anus through which feces is eliminated from the body.

Individuals should tell their physician if they have chicken pox or have been exposed to people who have chicken pox, have had any recent immunizations, have gout, heart disease, congestive heart failure, shingles, kidney stones, or liver disease. These diseases or conditions may affect the individual's reaction to bevacizumab.

During the time the individual is receiving treatment with bevacizumab, blood pressure should be monitored at least every two to three weeks and more frequently if it becomes elevated. Laboratory tests that measure the amount of protein in the urine should also be performed regularly. If blood pressure rises uncontrollably or protein in the urine increases excessively, the drug may be stopped.

Side effects

Serious but uncommon side effects may occur as the result of using bevacizumab. These serious side effects include:

- the development of perforations (holes) or abscesses in the colon
- inability of wounds to heal
- serious hemorrhage or internal bleeding, especially in individuals with lung cancer. Internal bleeding in the brain can result in stroke.
- blood clots in arteries
- uncontrolled high blood pressure (hypertension)
- kidney damage

More common but less serious side effects include but are not limited to:

- increased blood pressure that can be controlled with medication
- fatigue
- muscle weakness
- blood clots in veins
- diarrhea, nausea, loss of appetite
- low white blood cell count
- mouth sores
- increased protein in urine
- headache
- nosebleeds
- pain at the tumor site

Interactions

Although no formal drug interaction studies have as yet been completed it is important to review with a physician all prescription medications, over-the-counter medications, and herbal or alternative remedies that are being taken before treatment with bevacizumab is begun.

Tish Davidson, A. M.

Bexarotene

Definition

Bexarotene, also known by the brand name Targretin, is an antitumor agent of the class known as retinoids.

Purpose

Bexarotene is used to treat cutaneous T-cell lymphomas that have not responded to therapy with other drugs commonly used to treat this disease. Cutaneous T-cell lymphomas are characterized by tumors found on the skin and originate from cells of the immune system.

Description

Bexarotene is one of a group of drugs called retinoids, a derivative of vitamin A. Retinoids are involved with the process of stimulating some cells to mature to normal cells, and with inhibiting some cells from growing. It is thought that bexarotene binds to the retinoic acid receptors on cells. This binding ultimately results in the regulation of the growth and maturation of the cells.

KEY TERMS

Anorexia—Loss of appetite.

Lipids—Fatlike substances stored in the body that serve as a source of fuel and are important constituents of cell structure.

Photosensitivity—An abnormal cutaneous response to sunlight or filtered or artificial light.

Recommended dosage

Doses vary from individual to individual and depend on body weight and other factors. Bexarotene is taken by mouth in capsule form. The initial dose is usually 300 mg per square meter of body surface area per day. The maintenance dose is 300 to 400 mg per square meter of body surface area per day.

Precautions

Pregnant women should not take bexarotene. The risks of fetal abnormality are high, and women should take precautions to ensure they do not become pregnant.

Patients should limit their intake of vitamin A supplements to avoid additive toxic effects with bexarotene, which is a vitamin A derivative. Patients with diabetes and who are receiving insulin or oral medications for their diabetes are usually prescribed bexarotene with caution, and their blood sugar should be frequently monitored. Bexarotene may enhance the effects of the medications for diabetes, and patients may have low blood sugar levels.

Patients taking bexarotene may experience photosensitivity, or increased sensitivity to sunlight. In order to prevent rash, **itching**, or severe sunburn, patients should avoid direct sunlight exposure, avoid sunlamps or tanning beds, use sunblock lotion that is SPF 15 or greater, and wear a lip balm that is SPF 15 or greater. Patients should also wear sunglasses, a hat, and garments covering as much skin as possible when outside.

Side effects

The most common side effects of bexarotene increased levels of triglycerides, cholesterol, and high-density lipoprotein cholesterol. Some patients may require medications to control this rise in lipids. Decreased thyroid function also occurs frequently, and thyroid hormone replacement therapy may be necessary in some patients. Other common side effects include headaches, rash, red and scaly inflammation of the skin,

hair loss (**alopecia**), decreased red and white blood cells, and cataracts of the eyes. Patients should have eye examinations if they have any visual difficulties. Patients may be at increased risk of infections due to decreased white blood cells and experience **fatigue** due to decreased red blood cells. Other less common side effects include fluid gain causing swelling of extremities, insomnia, chills, **fever**, **anorexia**, **nausea and vomiting**, abdominal pain, back pain, flu-like symptoms, and dry skin. As with all medications, patients experiencing any of these (or other) side effects should notify their physician.

Interactions

There are an extremely large number of drugs that interact with bexarotene. Patients should consult their physician, nurse, or pharmacist about any medications they are taking before beginning a course of Bexarotene. Many physicians recommend bringing the containers with the names of all the drugs the patient is taking to their appointment with the physician.

Michael Zuck, Ph.D.

Bicalutamide *see* **Antiandrogens**

Bile duct cancer

Definition

Bile duct cancer, or cholangiocarcinoma, is a malignant tumor of the bile ducts within the liver (intrahepatic), or leading from the liver to the small intestine (extrahepatic). It is a rare tumor with poor outcome for most patients.

Description

Bile is a substance manufactured by the liver that aids in the digestion of food. Bile ducts are channels that carry the bile from the liver to the small intestine. Like the tributaries of a river, the small bile ducts in the liver converge into two large bile ducts called the left and right hepatic ducts. These exit the liver and join to form the common hepatic duct. The gallbladder, which concentrates and stores the bile, empties into the common hepatic duct to form the common bile duct. Finally, this large duct connects to the small intestine where the bile can help digest food. Collectively, this network of bile ducts is called the biliary tract.

Bile duct cancer originates from the cells that line the inner surface of the bile ducts. A tumor may arise anywhere along the biliary tract, either within or outside of the liver. Bile duct tumors are typically slow-growing tumors that spread by local invasion of neighboring structures and by way of lymphatic channels.

Demographics

Bile duct cancer is an uncommon malignancy. In the United States, approximately one case arises per 100,000 people per year, but it is more common in Southeast Asia. It occurs in men only slightly more often than in women. The most common time of diagnosis is during the fifth and sixth decades of life.

Causes and symptoms

A number of risk factors are associated with the development of bile duct cancer:

- Primary sclerosing cholangitis. This disease is characterized by extensive scarring of the biliary tract, sometimes associated with inflammatory bowel disease.
- Choledochal cysts. These are abnormal dilatations of the biliary tract that usually form during fetal development. There is evidence that these cysts may rarely arise during adulthood.
- Hepatolithiasis. This is the condition of stone formation within the liver (not including gallbladder stones).
- Liver flukes. Parasitic infection with certain worms is thought to be at least partially responsible for the higher prevalence of bile duct cancer in Southeast Asia.
- Thorotrast. This is a chemical that was previously injected intravenously during certain types of x rays. It is not in use anymore. Exposure to Thorotrast has been implicated in the development of cancer of the liver as well as the bile ducts.

Symptoms

Jaundice is the first symptom in 90% of patients. This occurs when the bile duct tumor causes an obstruction in the normal flow of bile from the liver to the small intestine. Bilirubin, a component of bile, builds up within the liver and is absorbed into the bloodstream in excess amounts. This can be detected in a blood test, but it can also manifest as yellowish discoloring of the skin and eyes. The bilirubin in the bloodstream also makes the urine appear dark. Additionally, the patient may experience generalized **itching** due to the deposition of bile components in the skin. Normally, a portion of the bile is excreted in stool; bile actually gives stool its brown

color. But when the biliary tract is obstructed by tumor, the stools may appear pale.

Abdominal pain, **fatigue**, **weight loss**, and poor appetite are less common symptoms. Occasionally, if obstruction of the biliary tract causes the gallbladder to swell enormously yet without causing pain, the physician may be able to feel the gallbladder during a physical examination. Sometimes the biliary tract can become infected, but this is normally a rare consequence of invasive tests. Infection causes **fever**, chills, and pain in the right upper portion of the abdomen.

Diagnosis

Certain laboratory tests of the blood may aid in the diagnosis. The most important one is the test for elevated bilirubin levels in the bloodstream. Levels of alkaline phosphatase and CA 19-9 may also be elevated.

When symptoms, physical signs, and blood tests point toward an abnormality of the biliary tract, then the next step involves radiographic tests. Ultrasound and **computed tomography** (CT scan) are noninvasive and rapid. These tests can often detect the actual tumor as well as dilatation of the obstructed biliary tract. If these tests indicate the presence of a tumor, then cholangiography is required. This procedure involves injecting dye into the biliary tract to obtain anatomic images of the bile ducts and the tumor. The specialist that performs this test can also insert small tubes, or stents, into a partially obstructed portion of the bile duct to prevent further obstruction by growth of the tumor. This is vitally important since it may be the only intervention that is possible in certain patients. Cholangiography is an invasive test that carries a small risk of infection of the biliary tract. The objective of these radiological tests is to determine the size and location of the tumor, as well as the extent of spread to nearby structures.

The treatment of bile duct tumors is usually not affected by the specific type of cancer cells that comprise the tumor. For this reason, some physicians forego **biopsy** of the tumor.

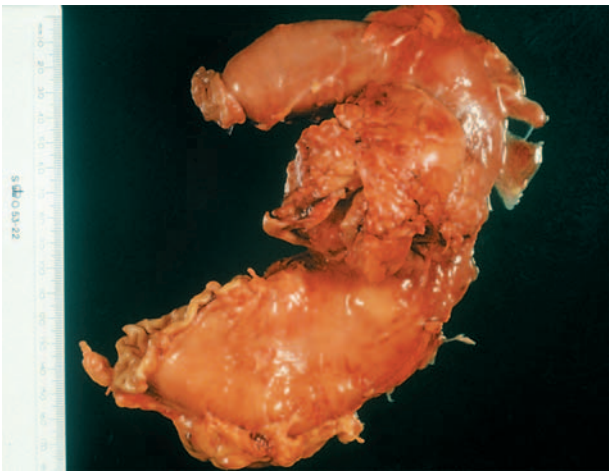
Treatment team

The treatment team may include the patient's primary physician, a surgeon, and a gastroenterologist who specializes in the **stenting** technique described above for palliation of bile duct strictures.

Clinical staging, treatments, and prognosis

Staging

Bile duct tumors are staged according to the tumor-node-metastasis (TNM) system of the **American Joint Commission on Cancer**. This staging scheme assesses the invasiveness of the tumor, the involvement of nearby lymph nodes, and the extent of distant **metastasis**.



Cancer of the bile duct. *(Copyright Biophoto Associates, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

- Stage I tumors are confined to the bile duct itself.
- Stage II tumors extend to the immediately adjacent tissues.
- Stage III tumors have spread to associated lymph nodes.
- Stage IV tumors have invaded local structures or have metastasized to distant structures. A higher stage signifies worse prognosis.

Treatment

The only hope for cure lies with surgical resection (removal) of the tumor and all involved structures. Unfortunately, sometimes the cancer has already spread too far when the diagnosis is made. Thus, in the treatment of bile duct cancer, the first question to answer is if the tumor may be safely resected by surgery with reasonable benefit to the patient. If the cancer involves certain blood vessels or has spread widely throughout the liver, then resection may not be possible. Sometimes further invasive testing is required.

Angiography can determine if the blood vessels are involved. **Laparoscopy** is a surgical procedure that allows the surgeon to directly assess the tumor and nearby lymph nodes without making a large incision in the abdomen. Only about 45% of bile duct cancers are ultimately resectable.

KEY TERMS

Angiography—Radiographic examination of blood vessels after injection with a special dye

Cholangiography—Radiographic examination of the bile ducts after injection with a special dye

Computed tomography—Radiographic examination by which images of cross-sectional planes of the body are obtained

Jaundice—Yellowish staining of the skin and eyes due to excess bilirubin in the bloodstream

Lymphatic—Pertaining to lymph, the clear fluid that is collected from tissues, flows through special vessels, and joins the venous circulation

Metastasis—The spread of tumor cells from one part of the body to another

Resection—To surgically remove a part of the body

Stent—Slender hollow catheter or rod placed within a vessels for duct to provide support or maintain patency

Ultrasound—Radiographic imaging technique utilizing high frequency sound waves

If the tumor is resectable, and the patient is healthy enough to tolerate the operation, then the specific type of surgery performed depends on the location of the tumor. For tumors within the liver or high up in the biliary tract, resection of part of the liver may be required. Tumors in the middle portion of the biliary tract can be removed alone. Tumors of the lower end of the biliary tract may require extensive resection of part of the pancreas, small intestine, and stomach to ensure complete resection.

Unfortunately, sometimes the cancer appears resectable by all the radiological and invasive tests, but is found to be unresectable during surgery. In this scenario, a bypass operation can relieve the biliary tract obstruction, but does not remove the tumor itself. This does not produce a cure but it can offer a better quality of life for the patient.

Chemotherapy and **radiation therapy** have not been proven effective in the treatment of bile duct cancer.

Prognosis

Prognosis depends on the stage and resectability of the tumor. If the patient cannot undergo surgical resection, then survival is expected to be less than one year. If the tumor is resected, survival improves but is still dismal. Only 20% of these patients survive past five years.

QUESTIONS TO ASK THE DOCTOR

- Has my cancer spread?
- What is the stage of my cancer and what does that mean for my prognosis?
- What treatment choices do I have?
- What are the risks or side effects of the treatment you recommend?
- What are the chances my cancer will come back after treatment?

Clinical trials

Studies of new treatments in patients are known as **clinical trials**. These trials seek to compare the standard method of care with a new method, or the trials may be trying to establish whether one treatment is more beneficial for certain patients than others. Sometimes, a new treatment that is not being offered on a wide scale may be available to patients participating in clinical trials, but participating in the trials may involve some risk. To learn more about clinical trials, patients can call the National Cancer Institute (NCI) at 1-800-4-CANCER or visit the NCI web site for patients at <http://www. cancertrials.nci.nih.gov>.

Prevention

Other than the avoidance of infections caused by liver flukes, there are no known preventions for this cancer.

Resources

BOOKS

Ahrendt, Steven A. and Henry A. Pitt. "Biliary Tract." In *Sabiston Textbook of Surgery*, edited by Courtney Townsend Jr., 16th ed. Philadelphia: W.B. Saunders Company, 2001, pp. 1076-1111.

"Cholangiocarcinoma." In *Clinical Oncology*, edited by Abeloff, Martin D., second ed. New York: Churchill Livingstone, 2000, pp.1722-1723.

ORGANIZATIONS

The American Cancer Society. Phone: 1-800-ACS 2345. Web site: <http://www.cancer.org>.

American Liver Foundation. Phone: 1-800-GO-LIVER (1-800-465-4837). Web site: <http://www.liverfoundation.org>.

National Cancer Institute Cancer Information Service. Phone: 1-800-4-CANCER. Web site: <http://www.nci.nih.gov>.

Kevin O. Hwang, M.D.

Biliary tract cancers *see* **Bile duct cancer; Gall bladder cancer**

Biology of cancer *see* **Cancer biology**

Biopsy

Definition

Biopsy is a diagnostic procedure in which a piece of tissue and/or cells are removed to be examined under a microscope by a pathologist.

Purpose

Biopsies are performed to determine the presence of cancer cells, establish **tumor grading**, and provide more information for treatment.

Precautions

Most biopsies should not be done on patients with blood clotting problems. If the patient has a low blood platelet count, a platelet transfusion can be given as a temporary relief measure, and a biopsy can then be performed. The physician should be notified of any bleeding problems—as well as any allergies, current medications, or pregnancy—well in advance.

Patients receiving IV sedation for a biopsy procedure will continue to feel drowsy for several hours, and should refrain from cooking, driving, or operating any equipment that requires careful attention. A ride home from the clinic should be arranged in advance.

Description

There are several different types of biopsies, and the decision on which one is most effective depends on where the tumor is located and the general health of the patient. Four common categories of biopsy are fine needle aspiration, core needle biopsy, excisional biopsy, and incisional biopsy.

Fine needle aspiration biopsy

Fine needle aspiration biopsy, also known as suction biopsy or needle aspiration biopsy, involves applying negative pressure through the use of a syringe and hollow, hypodermic needle. This type of biopsy is often used as a diagnostic procedure on neck and thyroid masses. It results in the removal of tissue that is fragmented into cells, as opposed to one sample of undamaged tissue. Fine needle aspiration biopsy is a frequently performed procedure that results in minimum discomfort and is less costly than many other types of biopsy.

Core needle biopsy

Core needle biopsy, also known as wide-core needle biopsy or cutting core biopsy, involves the use of a large-bore needle and is the simplest method of pathologic diagnosis of cancer. It results in minimal disturbance of surrounding tissues and a solid, intact sample. Tumors located in the liver and breast are commonly biopsied with this technique.

Incisional biopsy

This refers to the removal of part of the tumor from the larger tumor mass. An incisional biopsy is employed for tumors located deep within the body and after an initial needle biopsy has failed to supply enough tissue for diagnosis. Biopsies of this type are the preferred technique for diagnosing soft tissue cancers and osteosarcomas.

Excisional biopsy

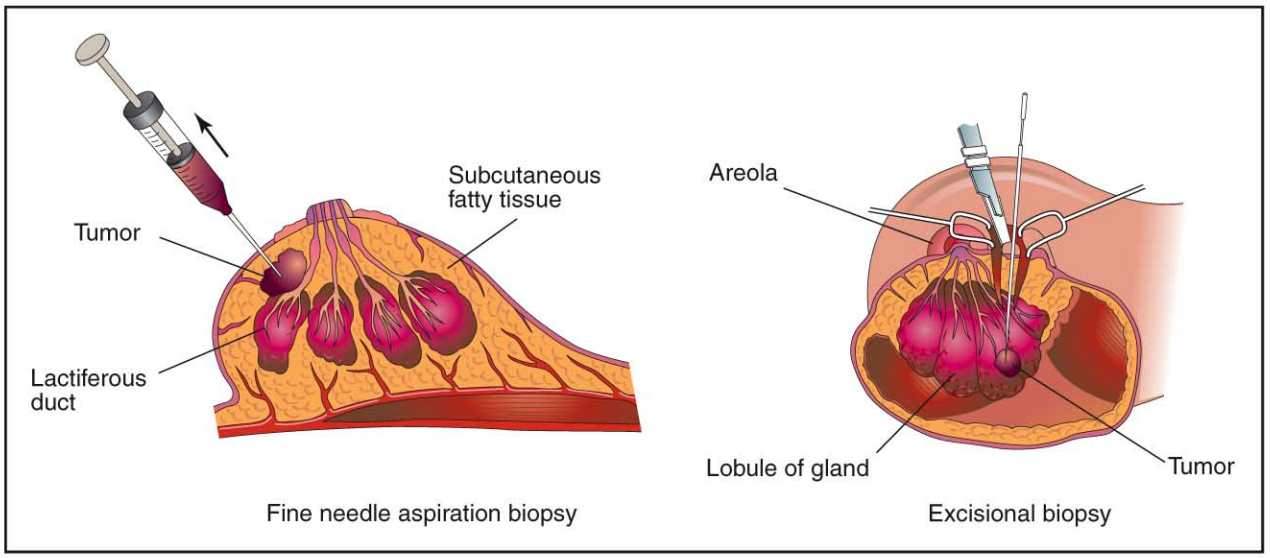
Also known as surgical biopsy, the excisional biopsy entails the surgical removal of the entire tumor mass and is a diagnostic technique that simultaneously serves as a treatment. For example, a **lumpectomy** removes the entire primary tumor mass associated with **breast cancer**. Excisional biopsy is also useful for diagnosing and removing surface tumors of the skin, such as those associated with squamous cell **carcinoma**, **basal cell carcinoma**, and malignant **melanoma**.

Preparation

Many biopsies can be performed in the doctor's office or in the hospital on an outpatient basis. Most do not require much special preparation on the part the patient, but patients should ask their physician for special instructions. Prior to the procedure, most require the use of anesthesia. Prior to and during a biopsy, special imaging techniques may be employed to assist in locating the tumor and guidance of biopsy procedures using a needle. Such imaging techniques include **computed tomography** scan (CT guided biopsy), fluoroscopy, **magnetic resonance imaging** (MRI), nuclear medicine scan, and ultrasound (ultrasound guided biopsy). Patients who undergo imaging scans may be injected with or asked to drink a contrast agent (dye) prior to biopsy.

Fine needle aspiration biopsy

Some routine blood work (blood counts, clotting profile) should be completed two weeks prior to biopsy.



Of the four different types of biopsy discussed, two are shown here: Fine needle aspiration biopsy and Excisional biopsy. A fine needle aspiration biopsy uses a very thin needle to withdraw fluid and cells from the growth to be examined. An excisional biopsy is a surgical procedure in which the entire area of concern and some surrounding tissue is removed for analysis. *(Illustration by Electronic Illustrators Group.)*

Patients may be asked not to eat for a specified time before the procedure. Those taking blood thinners (anticoagulants) or aspirin should talk to their physicians about whether they should discontinue using them prior to biopsy.

Core needle biopsy

Women undergoing breast biopsy should not wear talcum powder, deodorant, lotion, or perfume under their arms or on their breasts on the day of the procedure (since these may cause image artifacts or other problems). A comfortable two-piece garment should be worn. Patients may be asked not to eat for a specified time before the procedure. Those taking blood thinners or aspirin should talk to their physicians about whether they should discontinue using them prior to core needle biopsy.

Incisional biopsy

Patients should follow instructions provided by their doctor and give notification of any allergies. Those expecting general anesthesia should not eat or drink for at least 8 hours before an incisional biopsy. Patients should also bathe thoroughly before the procedure and allow time to rest afterward.

Excisional biopsy

Patients may be asked to: sign a consent form allowing the physician to perform this test; refrain from eating or drinking for at least 8 hours prior to surgery; and arrange for a ride home from the hospital (most patients can go home on the same day as the surgery). Those taking insulin, aspirin, non-steroidal anti-inflammatory drugs, or any medicines that affect blood clotting should notify their doctor well before the procedure.

Aftercare

Fine needle aspiration biopsy

After the biopsy, patients should be able to drive home, return to work, or perform any other routine activity. This biopsy does not affect medication schedules.

Core needle biopsy

Most patients can resume normal activities right after the biopsy. If there is excessive redness, pain, or drainage from the puncture site, patients should call their doctor immediately.

Incisional biopsy

After recovering from anesthesia, the patient will be observed for a few hours before returning home. During this time, an analysis may come back from the lab and the doctor may explain the nature of the abnormality. This analysis is the result of only one test and will not be 100% accurate. In about two days, lab testing should be complete. Patients should call their doc-

tor immediately if there is drainage from the wound or a **fever** develops.

Excisional biopsy

Depending on the invasiveness of the procedure, the patient may receive varied instructions for aftercare. The incision site should be kept clean, dry, and free of lotion, medication, or ointments. The patient may be required to remain in a certain position until sufficient time has passed to warrant the release of the patient from medical care. For example, patients are required to remain on their right side for approximately four hours to allow for healing to occur after a liver punch biopsy. Some patients, however, may be able to return to normal activities on the same day. Those who develop a fever, or notice bleeding, drainage, strong pain, or redness and warmth at the biopsy site should contact their doctor immediately.

Risks

Although most biopsies end with success, there are a certain number of risks to keep in mind. For example, complications can arise if other organs are nicked during a biopsy using a long needle. As with any procedure, there is a slight risk of allergic reaction to anesthesia. To be well informed, patients should consult with their physician about the risks prior to undergoing the procedure.

Fine needle aspiration biopsy

This biopsy poses no significant risks. Some minor bleeding may occur and some patients report a mild, dull, and throbbing sensation in the area of the biopsy, which usually subsides within 30 to 60 minutes. The risk of infection exists any time the skin is penetrated, but is extremely rare with this procedure. The error rate of diagnosis, however, is substantially higher than that of other biopsy procedures; major surgical resections should not be undertaken solely on the basis of the evidence of aspiration biopsy.

Core needle biopsy

A lumpy scar called a keloid may form in the area of puncture. Infection and bleeding may also occur at or under the biopsy site; however, this risk is uncommon. Core needle biopsy, like fine needle aspiration, only removes samples of a mass and not the entire area of concern. Therefore, it is possible that a more serious diagnosis may be missed by limiting the sampling of an abnormality.

Incisional biopsy

A keloid may form in the incision area. In rare cases, infection and bleeding may occur.

KEY TERMS

Contrast agent—A substance introduced into the body that allows radiographic visualization of certain tissues. Often used in MRI and CT imaging scans to emphasize the contrast between healthy and cancerous cells.

Excision—Surgical removal.

Incision—A surgical cut or gash.

Platelets—Small blood cells that play a role in the blood clotting process.

Tumor grading—Tumor grade refers to the degree of abnormality of cancer cells compared with normal cells. Establishing a grade allows the physician to determine further courses of treatment.

Excisional biopsy

Some patients may experience infection, bleeding, or bruising around the biopsy site. The physician should be consulted about any risks that may be related to a patient's medical history.

Normal results

The tissue sample obtained from the biopsy needs to be prepared for examination by a pathologist, and results usually are reported to the patient within a few days of the procedure. Normal (negative) results indicate that no malignancy is present.

Abnormal results

Abnormal results indicate that a malignancy or other abnormality is present. In some cases, results are indeterminate and patients are subject to further diagnostic procedures.

See also Bone marrow aspiration and biopsy; CT-guided biopsy; Liver biopsy; Pleural biopsy; Stereotactic needle biopsy.

Resources

BOOKS

Bast, Robert C., et al. *Cancer Medicine*. 5th ed. Hamilton, ON: B.C. Decker Inc., 2000.

OTHER

"An Alternative to Excisional Breast Biopsy: Core Needle Breast Biopsy." *Washington Radiology Associates*. [cited June 25, 2001]. <http://www.wrapc.com/corenedl.htm>.

QUESTIONS TO ASK THE DOCTOR

- Why is this particular type of biopsy being performed?
- Is there another type of biopsy that can be used?
- What are the risks associated with the biopsy?
- What level of discomfort is expected?
- Are there any special preparations associated with the biopsy?
- Are there any aftercare requirements?
- When are the results expected?
- Should a return visit be scheduled?

Harvard Health Online. [cited June 25, 2001]. <http://www.health.harvard.edu>.

National Cancer Institute. [cited June 25, 2001]. <http://www.nci.nih.gov>.

Sally C. McFarlane-Parrott

Bisacodyl *see* **Laxatives**

Bisphosphonates

Definition

Bisphosphonates are a class of drugs that lower calcium levels in the blood and can slow down bone loss that results from cancer or other causes.

Purpose

Bisphosphonates are used to slow down the loss of bone that results from **multiple myeloma** or from **breast cancer** that has spread, or metastasized, to the bones. These cancers cause bone to dissolve, in a process called resorption. This results in bone weakness and fractures. Bisphosphonates can prevent the holes that form in the bones from multiple myeloma. They can ease **bone pain** caused by cancer. They also help to prevent bone fractures and compression of the spinal cord, as well as the high calcium levels in the blood (**hypercalcemia**) caused by bone loss. Hypercalcemia can cause kidney failure and death. Bisphosphonates may help prevent breast cancer from spreading to the bones and other organs. **Clinical trials** are evaluating bisphosphonates for the treatment of bone metastases from other types of cancers.

Description

The most commonly used bisphosphonates are pamidronate disodium (APD; brand name Aredia) and etidronate disodium (EHDP; brand name Didronel). Both drugs are approved by the U.S. Food and Drug Administration. These drugs are classified as antihypercalcemics, meaning that they can lower blood calcium levels. They also are classified as bone resorption inhibitors, meaning that they can prevent bone from dissolving.

Other bisphosphonates include cladronate and alendronate. Cladronate is used less frequently because it is not completely absorbed by the digestive system and can cause stomach upset. Zoledronate and ibandronate are new, much more powerful bisphosphonates that are being evaluated, but are not yet available for routine use.

For cancer treatment, bisphosphonates may be used in conjunction with **chemotherapy**. Treatment with bisphosphonates may be accompanied by the injection of fluids into a vein (intravenous) so that large amounts of urine are excreted.

Recommended dosage

Pamidronate and etidronate are solutions that are injected into a vein. For the treatment of hypercalcemia, 30–90 mg of pamidronate are injected over a period of 2–24 hours. For the treatment of bone metastases from breast cancer, 90 mg are injected over a two-hour period every 3–4 weeks. For multiple myeloma, the 90-mg injection is over a four-hour period once a month. The usual dosage of etidronate is 7.5 mg per kg (3.4 mg per pound) of body weight, injected over two hours, for two or more days. The treatment may be repeated after at least one week off.

Etidronate also may be taken as a tablet, with water, on an empty stomach. The usual dosage for the treatment of hypercalcemia is 20 mg per kg (9.1 mg per pound) of body weight per day for 30 days. The maximum length of treatment usually is 90 days, but the treatment may be repeated after at least 90 days off of the drug. Cladronate is also taken as a pill.

Precautions

The amount of calcium in the diet may be important when taking bisphosphonates. Too much calcium in the diet may prevent absorption of oral etidronate. However, it is important to consume adequate amounts of calcium and vitamin D.

Other medical problems that may affect the use of bisphosphonates include:

- heart problems that may be aggravated by fluid retention
- kidney disease that could result in high levels of bisphosphonate in the blood
- intestinal problems or bowel disease, because etidronate can cause diarrhea
- bone fractures, particularly of the arm or leg, since etidronate can increase the risk of fractures

Bisphosphonates may cause allergic reactions in some individuals. Children may experience temporary changes in bone growth while being treated with etidronate and they should not take pamidronate. Older individuals may suffer from fluid retention if bisphosphonates are given with large amounts of fluid. Bisphosphonates should not be taken during pregnancy. It is not known whether these drugs pass into breast milk.

Side effects

Although bisphosphonates usually are well tolerated, some patients may experience side effects. The most common side effects include:

- **fatigue**
- **fever**
- nausea
- vomiting
- abdominal cramps
- low red blood cell levels (anemia)
- bone or joint pain
- muscle stiffness or pain
- pain or swelling at the site of injection or in the vein- However, some of these symptoms may result from the cancer or from other treatments for the cancer. A mild pain reliever can reduce or prevent the muscle and joint pain. Bisphosphonates that are taken by mouth can cause irritation and ulcers in the esophagus (the tube between the mouth and the stomach).

Additional side effects that may occur with pamidronate, particularly at dosages above 60 mg, include:

- chills
- confusion
- muscle spasms
- sore throat
- constipation
- decreased appetite

KEY TERMS

Antihypercalcemic—Drug that lowers the levels of calcium in the blood.

Hypercalcemia—High levels of calcium in the blood.

Metastasis—Spread of cancer from its point of origin to other parts of the body.

Resorption—Dissolving of bone, as with multiple myeloma or bone metastases from other cancers.

Additional side effects that may occur with etidronate include:

- decreased levels of magnesium and phosphorus in the blood
- **diarrhea**
- bone fracture, particularly of the thigh
- increases in test results for kidney function
- hives, skin rash, or **itching** (rare)
- swelling of the arms, legs, face, lips, tongue, or throat (rare)
- loss or altered sense of taste (with drug injection)

Interactions

Substances that may interact or interfere with bisphosphonates include:

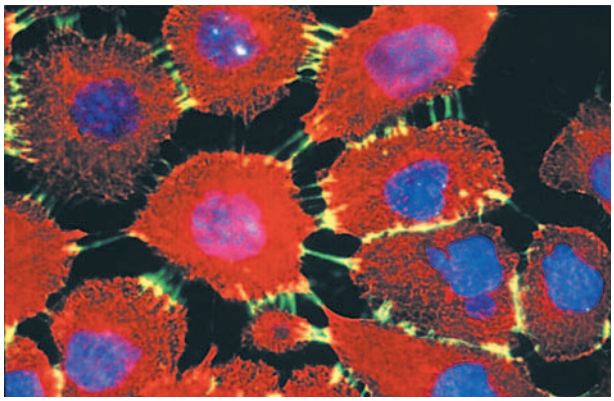
- mineral supplements, antacids, or other substances containing calcium, iron, magnesium, or aluminum, particularly if taken within two hours of taking etidronate
- substances containing vitamin D

Margaret Alic, Ph.D.

Bladder cancer

Definition

Bladder cancer is a disease in which the cells lining the urinary bladder lose the ability to regulate their growth and start dividing uncontrollably. This abnormal growth results in a mass of cells that form a tumor.



An immunofluorescent light micrograph of cells cultured from squamous carcinoma of the bladder. *(Photograph by Nancy Kedersha, Photo Researchers, Inc. Reproduced by permission.)*

Description

The urinary bladder is a hollow muscular organ that stores urine from the kidneys until it is excreted out of the body. Two tubes called the ureters bring the urine from the kidneys to the bladder. The urethra carries the urine from the bladder to the outside of the body.

Bladder cancer has a very high rate of recurrence following treatment. Even after superficial tumors are completely removed, there is a 75% chance that new tumors will develop in other areas of the bladder. Patients need very frequent and thorough follow-up care. When detected at the early stages, the prognosis for bladder cancer is excellent. At least 94% of patients survive five years or more after initial diagnosis. If the disease has spread to the nearby tissues, however, the survival rates drop to 49%. If it has metastasized to distant organs such as the lung or liver, only 6% of patients will survive five years or more.

Demographics

Bladder cancer is the sixth most common cancer in the United States. The American Cancer Society (ACS) estimated that in 2001, approximately 54,300 new cases of bladder cancer would be diagnosed (about 39,200 men and 15,100 women), causing approximately 12,400 deaths.

The highest occurrences of bladder cancer are found in industrialized countries such as the United States, Canada, France, Denmark, Italy, and Spain. In all countries, the incidence of bladder cancer is higher for men than women. Among men, the highest rates occur in white non-Hispanic males (33.1 per 100,000). The rates for men of African descent and Hispanic men are similar and are approximately one-half of the rate among white non-Hispanic men. The lowest rate of bladder cancer occurs in the Asian population. Among women, the highest rates also occur in white non-Hispanic females and are approximately twice the rate for Hispanics. Women of African descent have higher rates of bladder cancer than Hispanic women.

Age is also an important factor: bladder cancer is significantly more common in older men and women in all populations. Bladder cancer rates for people aged 70 years and older are two to three times higher than for people in the 55 to 69 age group, and approximately 15 to 20 times higher than for people between the ages of 30 and 54.

Causes and symptoms

Although the exact cause of bladder cancer is not known, smokers are twice as likely to get the disease as are nonsmokers. Smoking is subsequently considered to be the greatest risk factor for bladder cancer. Workers who are exposed to certain chemicals that are used in the dye, rubber, leather, textile, and paint industries are also believed to be at a higher risk for bladder cancer.

Frequent urinary infections, kidney and bladder stones, and other conditions that cause long-term irritation to the bladder may increase the risk of getting bladder cancer. A past history of tumors in the bladder also increases one's risk of developing new tumors.

One of the first warning signals of bladder cancer is blood in the urine. There may be enough blood in the urine to change its color to a yellow-red or dark red. At other times, the color of the urine appears normal but chemical testing of the urine reveals the presence of blood cells. Painful urination, increased frequency, and increased urgency (the sensation of having to urinate immediately but being unable to do so) are other possible signs of bladder cancer. All of these symptoms may also be caused by conditions other than cancer, so it is important to see a doctor to have the symptoms evaluated.

In 2003, studies showed that hormone replacement therapy (HRT), a treatment used by many postmenopausal women, significantly increased the risk of bladder and other cancers.

Diagnosis

If a doctor has any reason to suspect bladder cancer, several tests may be used to find out if the disease is present. A complete medical history will be taken to check for any risk factors. A thorough physical examination will be conducted to assess all the signs and symp-

toms. Laboratory testing of a urine sample will help to rule out the presence of a bacterial infection. In a urine **cytology** test, the urine is examined under a microscope to look for any abnormal or cancerous cells. A catheter (tube) can be advanced into the bladder through the urethra and a salt solution passed through it to wash the bladder. The solution can then be collected and examined under a microscope to check for the presence of any cancerous cells.

A test known as the intravenous pyelogram (IVP) is an x-ray examination performed after a dye is injected into a vein in the arm. The dye travels through the blood stream and reaches the kidneys to be excreted, clearly outlining the kidneys, ureters, bladder, and urethra. Multiple x rays are taken to detect any abnormalities in the lining of these organs.

The physician may use a procedure known as a **cystoscopy** to view the inside of the bladder. A thin hollow lighted tube is introduced into the bladder through the urethra. If any suspicious-looking masses are seen, a small piece of the tissue can be painlessly removed using a pair of **biopsy** forceps. The tissue is then examined microscopically to verify if cancer is present, and if so, the type of cancer will be identified.

If cancer is detected and there is evidence showing that it has metastasized to distant sites in the body, imaging tests such as chest x rays, **computed tomography** (CT) scans, and **magnetic resonance imaging** (MRI) may be done to determine which organs are affected. Bladder cancer tends to spread to the lungs, liver, and bone.

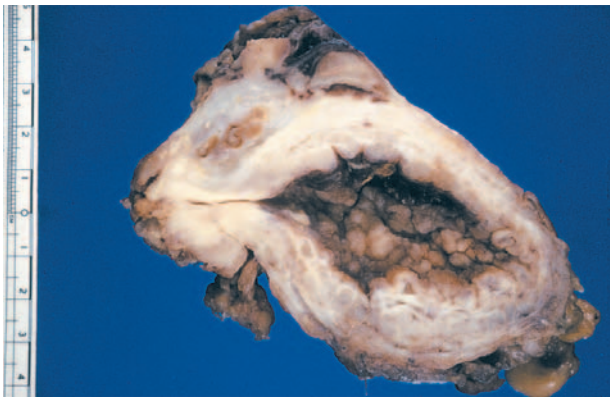
Treatment team

Treatment for bladder cancer depends on the stage of the disease and how deeply the cancer has penetrated the bladder wall. It also depends on the grade of the cancer and on the patient's general health status and personal preferences. Most likely, a team of specialists including a urologist, an oncologist, a surgeon, and a radiation oncologist will be responsible for treatment. The treatment team will develop a plan tailored to the individual patient and may recommend one treatment method or a combination of methods.

Clinical staging, treatments, and prognosis

Staging

The following stages are used by health care providers to classify the location, size, and spread of the cancer, according to the TNM (tumor, lymph node, and metastases) staging system:



Excised specimen of a cancerous human bladder, showing a large tumor mass. *(Copyright Science Photo Library, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

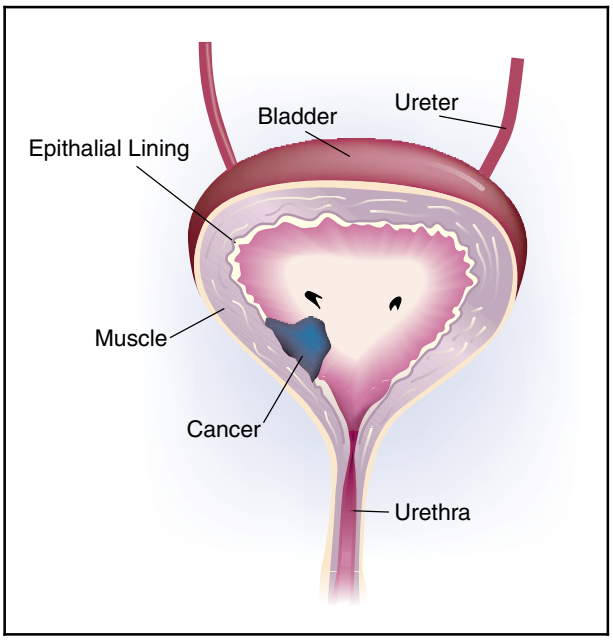
- Stage 0: Cancer is found only on the inner lining of the bladder (a noninvasive **carcinoma**).
- Stage I: Cancer has spread to the layer of tissue beyond the inner lining of the bladder but not to the bladder muscles.
- Stage II: Cancer has spread to the muscles in the bladder wall but not to the fatty tissue surrounding the bladder.
- Stage III: Cancer has spread to the fatty tissue surrounding the bladder and potentially to the prostate, vagina, or uterus, but not to the lymph nodes or other organs.
- Stage IV: Cancer has spread to the lymph nodes, pelvic or abdominal wall, and/or other organs.
- Recurrent: Cancer has recurred in the bladder or at another site after having been treated.

Standard treatments

The three standard modes of treatment that are available for bladder cancer are surgery, **radiation therapy**, and **chemotherapy**.

Surgery is considered to be an option only when the disease is in its early stages. If the tumor is localized to a small area and has not spread to the outer layers of the bladder, then the surgery is done without entering the abdomen. A cystoscope is introduced into the bladder through the urethra, and the tumor is removed. This procedure is called a transurethral resection (TUR). Passing a high-energy laser beam through the cystoscope to burn cancer cells, a procedure known as electrofulguration, may treat any remaining cancer.

If the cancer has invaded the wall of the bladder, surgery will be done through an incision in the abdomen.



Bladder cancer on the inner lining of the bladder. *(Illustration by Argosy Publishing Inc. Reproduced by permission of The Gale Group.)*

Cancer that is not very large can be removed by partial cystectomy, a procedure where a part of the bladder is removed. If the cancer is large or is present in more than one area of the bladder, a radical cystectomy is done. The entire bladder is removed in this procedure; adjoining organs may also be removed. In men, the prostate is removed, while in women, the uterus, ovaries, and fallopian tubes are removed.

If the entire urinary bladder is removed, then an alternate storage place must be created for urine before it is excreted out of the body. To do this, a piece of intestine is converted into a small bag and attached to the ureters. This is connected to an opening (stoma) that is made in the abdominal wall. The procedure is called a **urostomy**. In some urostomy procedures, the urine from the intestinal sac is routed into a bag that is placed over the stoma in the abdominal wall. The bag is hidden by clothing and has to be emptied occasionally by the patient. In a different procedure, the urine is collected in the intestinal sac, but there is no bag on the outside of the abdomen. The intestinal sac has to be emptied by the patient by placing a drainage tube through the stoma.

Radiation therapy that uses high-energy rays to kill cancer cells is generally used after surgery to destroy any remaining cancer cells. If the tumor is in a location that makes surgery difficult or if it is large, radiation may be used before surgery to shrink the tumor. In

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Chemotherapy—Treatment with drugs that selectively destroy cancer cells.

Computed tomography (CT) scan—A medical procedure in which a series of x rays are taken and analyzed by a computer in order to form detailed pictures of areas inside the body.

Cystoscopy—A diagnostic procedure in which a hollow lighted tube (cystoscope) is used to look inside the bladder and the urethra.

Electrofulguration—A procedure in which a high-energy laser beam is used to burn the cancerous tissue.

Immunotoxins—Antibodies produced in the laboratory that recognize specific substances that are more abundant in cancer cells than in normal cells; immunotoxins identify cancer cells and deliver a powerful toxin that kills the cells.

Intravenous pyelogram (IVP)—A procedure where an injected dye outlines the urinary system on an x ray to help reveal potential abnormalities.

Magnetic resonance imaging (MRI)—A medical procedure used for diagnostic purposes where pictures of areas inside the body can be created using a magnet linked to a computer.

Partial cystectomy—A surgical procedure where the cancerous tissue is removed by cutting out a small piece of the bladder.

Photodynamic therapy—A combination of special light rays and drugs that are used to destroy the cancerous cells.

Radiation therapy—Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Radical cystectomy—A surgical procedure that removes the entire bladder and occasionally other adjoining organs.

Stoma—An artificial opening between two cavities or between a cavity and the surface of the body.

Transurethral resection— A surgical procedure to remove abnormal tissue from the bladder using an instrument called a cystoscope.

Urostomy—A surgical procedure in which the ureters are disconnected from the bladder and connected to an opening (see stoma) on the abdomen, allowing urine to flow into a collection bag.

QUESTIONS TO ASK THE DOCTOR

- Why do I need to have a biopsy?
- How long will it take? Will I be awake? Will it hurt?
- How soon will I know the results?
- If I do have bladder cancer, who will talk with me about treatment? When?

cases of advanced bladder cancer, radiation therapy is used to ease the symptoms such as pain, bleeding, or blockage. External beam radiation focuses a beam of radiation on the area of the tumor. Alternatively, a small pellet of radioactive material may be placed directly into the cancer. This is known as interstitial radiation therapy.

Chemotherapy uses anticancer drugs to destroy the cancer cells that may have migrated to distant sites. The drugs are injected into the patient intravenously or taken orally in pill form. Generally a combination of drugs is more effective than any single drug in treating bladder cancer. Chemotherapy may be given following surgery to kill any remaining cancer cells. Called neoadjuvant chemotherapy, this treatment may allow people with bladder cancer to live up to 31 months longer than previous treatments allowed. Chemotherapy also may be given even when no remaining cancer cells can be seen (adjuvant chemotherapy). Anticancer drugs, including **thiotepa**, **doxorubicin**, and mitomycin, may also be instilled directly into the bladder (intravesicular chemotherapy) to treat superficial tumors. In 2003, the FDA was giving fast track designation to a form of paclitaxel, a common anticancer drug, that was shown effective in treating metastatic or locally advanced bladder cancer.

Immunotherapy or biological therapy uses the body's own immune cells to fight the disease. To treat superficial bladder cancer, **bacillus Calmette-Guérin** (BCG) may be instilled directly into the bladder. BCG is a weakened (attenuated) strain of the tuberculosis bacillus that stimulates the body's immune system to fight the cancer. This therapy has been shown to be effective in controlling superficial bladder cancer.

A 2003 report stated that giving patients with bladder cancer chemotherapy followed by surgery may improve their outcomes. In the study of 307 patients, those with this combination of therapy lived two years longer than those treated with surgery only.

Photodynamic treatment is a novel mode of treatment that uses special chemicals and light to kill the cancerous cells when the bladder cancer is in its early stages. First, a drug is introduced into the bladder that makes the cancer cells more susceptible to light. A special light is then shone on the bladder in an attempt to destroy the cancerous cells.

Alternative and complementary therapies

Gene therapy is a new method being tested as a complementary therapy for bladder cancer. Research has shown that mutations in tumor suppressor genes can cause abnormal growth of bladder cells. Gene therapy involves infecting bladder cancer cells with specially designed viruses that contain a normal gene in order to restore a normal cell growth process.

Immunotherapy is another area that is expected to contribute new complementary treatment methods. Immunotoxins are antibodies produced in the laboratory that recognize specific substances that are more abundant in cancer cells than in normal cells. Once the immunotoxins identify a cancer cell, they deliver a powerful toxin attached to the antibody that enters and kills the cell.

Coping with cancer treatment

As with any cancer, shock and stress are natural reactions to a confirmed bladder cancer diagnosis. Coping is often made easier with access to helpful information and support services. Many patients want to learn all they can about the disease and their treatment choices so as to be fully involved in the decisions that are being made concerning their medical care. National cancer organizations are an important source of medical information. Many associations have also been organized to allow patients the opportunity to meet others undergoing similar experiences in support groups.

Patients are often uncomfortable during the first few days after bladder surgery. They may also experience **fatigue** and weakness. Those undergoing radiation therapy or chemotherapy may experience side effects such as pain, fatigue, rashes, or bleeding. Pain can be controlled with medication and patients should feel free to discuss aspects of pain relief with their physician or nurse.

Clinical trials

In 2001 the National Cancer Institute (NCI) supported over 50 bladder cancer **clinical trials** to evaluate a variety of anticancer drugs. Some trials study new treatments involving radiation therapy, chemotherapy,

biological therapies, and new combinations of various therapies. Other trials study ways to lower the side effects of treatment. Patients who take part in these studies often have the chance to benefit from promising new drugs and developments. Those interested in taking part in a trial should discuss the possibility with their physician and consult an NCI booklet entitled, "Taking Part in Clinical Trials: What Cancer Patients Need To Know" (NIH Publication #97-4250).

Prevention

Since it is not known what exactly causes bladder cancer, there is no certain way to prevent its occurrence. Avoiding risk factors whenever possible is the best alternative. Since smoking doubles one's risk of getting bladder cancer, avoiding tobacco may prevent at least half the deaths that result from bladder cancer. Taking appropriate safety precautions when working with organic cancer-causing chemicals is another way of reducing one's risk.

Those with a history of bladder cancer, kidney stones, urinary tract infections, and other conditions that cause long-term irritation to the bladder are advised to undergo regular screening tests such as urine cytology, cystoscopy, and x rays of the urinary tract, so that cancer may be detected at an early stage and treated appropriately.

Special concerns

Special concerns may arise for those who have undergone partial or radical cystectomy. For example, if the bladder has to be removed, the patient will need to learn a new way to store and pass urine. Women who have had a radical cystectomy are not able to have children because their uterus has also been removed. Men who have had a radical cystectomy will become impotent (unable to sustain an erection) if their prostate and seminal vesicles have also been removed.

See also Metastasis; Intravenous urography; Tumor staging.

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Bleomycin

Definition

Bleomycin (Blenoxane) kills cancer cells by damaging the genetic material known as DNA, thus preventing cells from repairing themselves.

Purpose

Bleomycin is used in the treatment of a number of different cancers, including cancer of the head and neck, skin, esophagus, lung, testis, penis, vulva, cervix, and genitourinary tract. In addition, it is used in the treatment of **Hodgkin's disease** and **non-Hodgkin's lymphomas**. It may also be used to treat **Kaposi's sarcoma**.

Because bleomycin is used in the treatment of so many different cancers, only a sampling of its uses can be provided here. In the treatment of Hodgkin's disease, one **chemotherapy** regimen used is the so-called ABVD, which consists of **doxorubicin**, bleomycin, **vinblastine**, and **dacarbazine**. Another regimen is called MOPP/ABV, which consists of **mechlorethamine**, **vincristine**, prednisone, **procarbazine**, doxorubicin, bleomycin, and vinblastine.

A treatment used for stage III and IV non-Hodgkin's **lymphoma** is the CHOP-bleomycin regimen, which consists of **cyclophosphamide**, hydroxydaunomycin, vincristine, prednisone, and bleomycin. Another approach to the same illness involves the m-BACOD chemotherapy regimen, which consists of **methotrexate**, bleomycin, doxorubicin, cyclophosphamide, vincristine, and **dexamethasone**. Yet another approach to treating this disease is called ProMACE-CytaBOM, and consists of cyclophosphamide, doxorubicin, **etoposide**, prednisone, **cytarabine**, bleomycin, vincristine, methotrexate, and **leucovorin**.

Description

Bleomycin is an antitumor antibiotic that fights cancer by attacking the DNA in cancerous cells, thus interfering with cell growth.

Recommended dosage

A dose of 0.25-0.50 units/kg (10-20 units per square meter) is given once or twice a week either intravenously, intramuscularly, or subcutaneously. A small test dose should be given first to test for a possible severe allergic reaction.

Precautions

Patients who receive certain forms of oxygen therapy while taking bleomycin or who receive anesthesia while taking bleomycin are at increased risk for developing serious lung problems.

Patients given bleomycin may develop an acute allergic reaction that may be fatal in rare cases. Therefore, a patient should only receive a small test dose of bleomycin the first time the drug is administered. After this initial dose the patient is observed carefully for one hour. Assuming no further problems appear, the patient may then receive a standard dose.

The likelihood that lung damage will occur increases if a patient receives more than 450–500 units of the drug during an entire lifetime. So, it is prudent to limit the amount of this medication given. Furthermore, it may be unwise to give bleomycin in regimens containing cyclophosphamide, as this combination also increases the likelihood that lung damage will occur.

KEY TERMS

DNA—DNA is a nucleic acid found inside of cells that carries genetic information.

Raynaud's phenomenon— Raynaud's phenomenon, which affects the fingers and toes, may involve pain, pale color, and abnormal sensation (e.g., burning or prickling).

Side effects

Lung problems are a serious side effect affecting some patients who receive bleomycin. While lung problems can appear regardless of how much of the medicine is given, they are more likely to appear if a patient receives more than a certain amount of the medicine—250 units according to some authorities and 450–500 units according to others. The appearance of a dry cough may indicate the development of lung problems. Lung damage can be assessed by measuring the rate at which the patient is able to transfer gas across the lung membranes (DLCO or diffusion lung capacity).

Other side effects of bleomycin may include skin problems and alteration of skin color, allergic reactions, Raynaud's phenomenon, and hair loss (**alopecia**). In addition, headache, and **nausea and vomiting** may occur. Rheumatoid arthritis may worsen during bleomycin therapy. Patients with testicular tumors who receive multiple chemotherapy agents including bleomycin may develop Raynaud's phenomenon and cardiovascular disease. Raynaud's phenomenon, which affects the fingers and toes, may involve pain, pale color, and abnormal sensation (for instance, burning or prickling).

Approximately 1 out of every 100 patients who takes bleomycin experiences a reaction that involves chills, **fever**, wheezing, low blood pressure, and mental confusion. Unlike many other cancer drugs, bleomycin is not likely to cause any damage to the bone marrow.

Patients may be given steroids before bleomycin therapy is started in an effort to reduce the side effects of the drug.

Interactions

Bleomycin is often given in combination with with other anticancer drugs, for example **cisplatin**, vinblastine, and etoposide. Such combinations have been found to be more effective than single drug therapy.

Bob Kirsch

Blood dyscrasias *see* **Multiple myeloma; Waldenstrom's macroglobulinemia**

Blood transfusion *see* **Transfusion therapy**

Body image/self image

Description

Body image refers to a person's internal picture of his or her external physical appearance. Self image is a broader category that refers to one's inner perception of his or her physical, mental, interpersonal, and spiritual characteristics and abilities. The distinction is important because cultures vary significantly regarding the amount of emphasis given to body image as one aspect of self image. In Japan, for example, body image is a much smaller part of most people's self-image than it is in the United States. Both forms of self-perception, however, may be affected by cancer treatment.

Specific body image or self image concerns vary according to age and gender. Children being treated for cancer have different issues from adults because their self and body images are still being formed. Children and adolescents with cancer sometimes internalize a pictureof themselves as disfigured or unattractive, or as physically weak and incompetent. Even when the cancer has been successfully treated, the child's self image may still reflect feelings of being "sick" or "damaged." A distorted self image in turn can cause difficulties in social relationships as the child grows older. The Candlelighters programs offer practical advice and social support for children with cancer and their families.

Self image problems in adults tend to reflect (and reinforce) American society's patterns of gender socialization. Studies indicate that many women tend to be openly concerned about damage to their external appearance caused by cancer treatments. For many women, anxiety about losing their looks is directly related to fear of losing their husband or partner. Men's concern about outward appearance is less obvious but may be expressed as a need to look "healthy" in order to keep their job. Although there are not as many studies of men's reactions to cancer treatment as there are of women's, recent research indicates that men are still more concerned about losing physical strength or specific physical abilities required by their work than about their looks as such.

Causes

Cultural context

It is important to situate body image/self image issues related to cancer treatment within the larger context of contemporary emphasis on physical perfection. Advertising in the mass media encourages people to feel dissatisfied with their bodies. One study of the effects of television advertising on college youth found that as little as half an hour of ideal-body commercials has a negative impact on a person's body image. Another study found that a majority of American adults, men as well as women, believe that people are judged on the basis of appearance first and talent or personality second. In a cultural setting in which healthy people often feel they cannot measure up to media standards of attractiveness, it is not surprising that cancer patients are concerned about the effects of therapy on their appearance.

In addition to concerns about appearance, some cancer patients experience a loss of adult identity related to the need to relearn bowel and bladder habits. Patients with colorectal cancer and others who have stomas must undergo a second period of toilet training as adults. Many of these patients report that their ability to travel, work, or socialize with others is significantly impaired by their problems with bowel control. According to a Swedish study, these difficulties often affect the patient's spouse as well in terms of limitations on the couple's social life.

Surgery

Surgery on the face or the parts of the body associated with sexual performance or attractiveness has a more severe impact on self image than surgery on the hands, feet, or back. Breast surgery in women and surgical treatment of **prostate cancer** in men are often accompanied by changes in the patient's self image, particularly with respect to sexual relations. Sexual responsiveness can also be affected if the surgeon has had to remove tissue containing nerve endings that are sensitive to touch.

Radiation and chemotherapy

Radiation and **chemotherapy** can affect a cancer patient's body image because they often cause hair loss,

radiation burns, and unattractive changes in the patient's complexion. While hair loss caused by chemotherapy is usually a temporary condition, hair loss caused by radiation treatment may be permanent. In addition, both radiation and chemotherapy can cause nausea, vomiting, fatigue, **depression**, and other reactions that affect the patient's sense of competence as well as their relationships with others. Self image often suffers when a person feels that job performance and valued relationships are being strained by these side effects of cancer treatment.

Treatments

Cosmetic

Since 1989, the American Cancer Society, the Cosmetic, Toiletry, and Fragrance Association Foundation, and the National Cosmetology Association have sponsored the "Look Good... Feel Better" (LGFB) program, which offers classes in a number of medical centers. These classes help female cancer patients with self image issues as well as teaching them special grooming techniques to manage the side effects of cancer therapy. LGFB has been available in Canada since 1992.

Hair loss can be covered by a variety of wigs, partial hairpieces, and scarves or turbans. The American Hair Loss Council offers more detailed information about these and other ways to cope with hair loss caused by cancer treatment. Doctors who specialize in plastic surgery can suggest ways to treat facial scars or other types of surgical disfigurement, including the loss of body parts. A prosthesis, which is an artificial replacement for a missing or damaged body part, can be made to order for the patient.

Counseling and support

Cancer patients who are experiencing serious emotional problems related to changes in appearance may benefit from counseling or support groups. Individual psychotherapy guides people to look at the reasons for focusing on their looks as well as ways to cope with the changes. Pastoral or spiritual counseling can help remind patients that they are more than just their bodies. Support groups for cancer patients are good places to share feelings and useful tips about dress and grooming with others who are in the same situation.

Alternative and complementary therapies

Alternative and complementary therapies may help patients to deal with changes in self and body image through developing a fuller self image, finding new interests, or learning new skills. Meditation and prayer can help patients put physical appearance inside a larger framework of values. Some cancer patients find yoga, t'ai chi, and dance or movement therapy are interesting to learn as well as good forms of exercise. In addition, a group of researchers at Brown Medical School reported in early 2004 that cancer survivors who exercise regularly have higher levels of energy and self-esteem, and lower levels of depression and other mood disturbances, than survivors who do not exercise.

Lastly, massage, calming or uplifting music, and aromatherapy allow patients to balance the side effects of cancer treatment with relaxing and pleasant experiences.

See also Alopecia; Sexuality.

KEY TERMS

Body image—A term that refers to a person's inner picture of his or her outward appearance.

Prosthesis (plural, prostheses)—An artificial substitute for a missing or defective body part. Prostheses are usually designed to look and feel as natural as possible.

Self image—A wider term that includes a person's perception of his or her talents, character traits, interests, spirituality, and other aspects of their being as well as outward physical appearance.

Stoma—A surgical opening made in an organ or in the abdominal wall that allows digestive wastes to pass into another part of the intestines or directly to the outside of the body.

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Bone marrow aspiration and biopsy

Definition

Bone marrow aspiration, also called bone marrow sampling, is the removal by suction of fluid from the soft, spongy material that lines the inside of most bones. Bone marrow **biopsy**, or needle biopsy, is the removal of a small piece of bone marrow.

Purpose

Bone marrow aspiration is used to:

- pinpoint the cause of abnormal blood test results
- confirm a diagnosis or check the status of severe **anemia** (abnormally low numbers of red blood cells in the bloodstream) of unknown cause, or other irregularities in the way blood cells are produced or become mature
- evaluate abnormalities in the blood's ability to store iron
- diagnose infection

Bone marrow biopsy is used to:

- obtain intact bone marrow for laboratory analysis
- diagnose and stage some types of cancer or anemia and other blood disorders
- identify the source of an unexplained fever
- diagnose fibrosis of bone marrow or **myeloma** (a tumor composed of cells normally found in the bone marrow) when bone marrow aspiration has failed to provide an appropriate specimen

Bone marrow aspiration and bone marrow biopsy are also used to gauge the effectiveness of **chemotherapy** and other medical treatments. These procedures are often used together to ensure the availability of the best possible bone marrow specimen.

Precautions

Allergies or previous adverse reactions to medications should be discussed with the doctor. Any current medications, including herbal or nutritional supplements, should be evaluated for the potential to interfere with proper coagulation (clot formation). These would include coumadin, aspirin, and other agents used as blood thinners. Caution should be used when the herbs gingko, ginger, garlic, or ginseng have been utilized as supplements, due to a risk of bleeding.

Pregnancy, lactation (production and secretion of milk), and preexisting platelet or bleeding disorders should be evaluated before either procedure is undertaken.

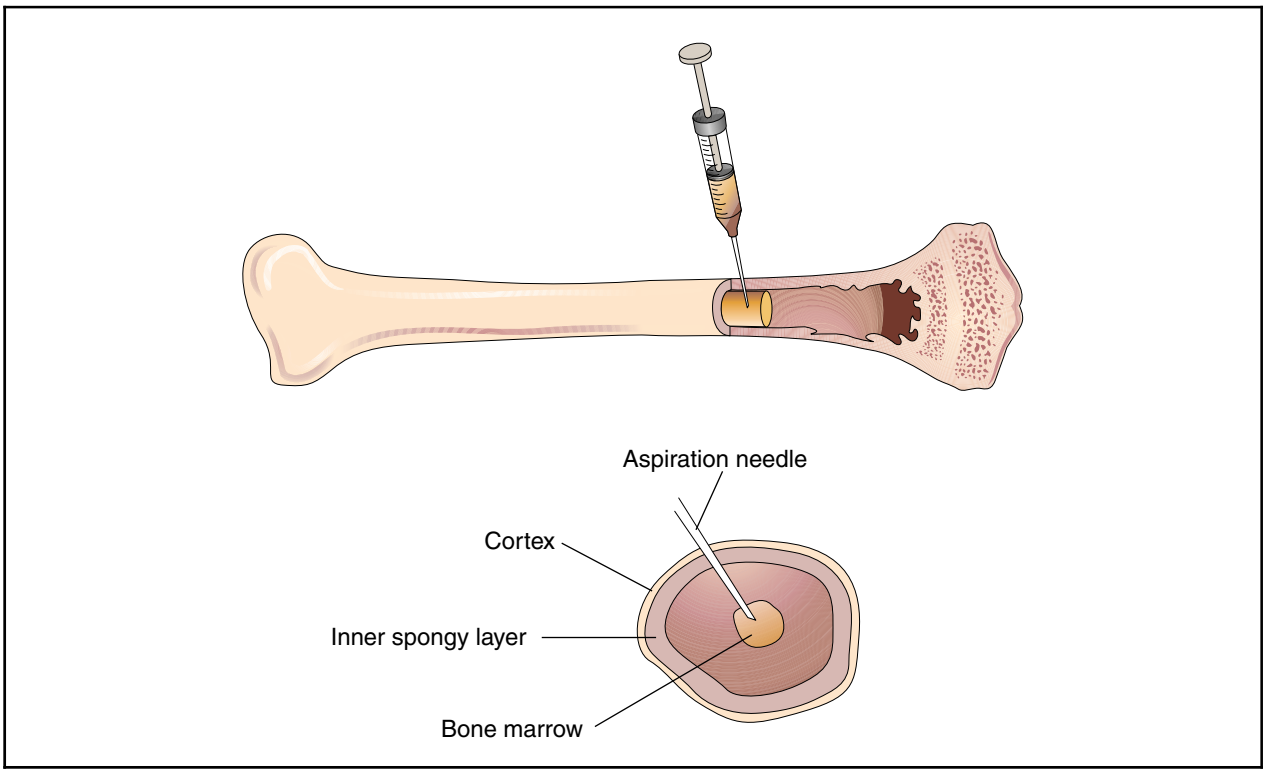
Description

Bone marrow aspiration and biopsy should be performed by a physician or nurse clinician. Each procedure takes about 20 to 30 minutes and is usually performed on an outpatient basis, but can be done in a hospital if necessary.

The skin covering the biopsy site is cleansed with an antiseptic, and the patient may be given a mild sedative. A local anesthetic is administered. The hematologist or nurse clinician performing the procedure will not begin until the anesthetic has numbed the area from which the specimen is to be extracted. In both adults and children, aspiration and biopsy are most commonly performed on the rear bone of the hip (posterior iliac crest). In adults, sampling from the sternum (breastbone) is sometimes done. The latter location is technically easier, but is somewhat more painful for the patient and presents the risk of heart injury. On rare occasions, a long bone of the leg (tibia) may be used as a sample site for an infant.

In a bone marrow aspiration, a special needle is inserted beneath the skin and rotated until it penetrates the cortex, or outer covering of the bone. At least half a teaspoon of marrow is withdrawn from the bone by a syringe attached to the needle. The patient may experience discomfort when the needle is inserted or when the marrow is aspirated. If more marrow is needed, the needle is repositioned slightly, a new syringe is attached, and a second sample is taken. The samples are transferred from the syringes to slides and vials, then sent to a laboratory for analysis.

Bone marrow biopsy may be performed immediately before or after bone marrow aspiration. The procedure utilizes a special large-bore needle that is used to drill out a core of marrow. In bone marrow biopsy, the needle is inserted, rotated from side to side, withdrawn, and reinserted at a different angle. This procedure is repeated if needed until a small core, about 0.4 inches (1 cm) long, is separated from the bone marrow. The needle



In a bone marrow aspiration, a needle is inserted beneath the skin and rotated until it penetrates the cortex, or outer covering, of the bone. A small amount of marrow is suctioned out of the bone by a syringe attached to the needle. *(Illustration by Electronic Illustrators Group. Reproduced by permission of The Gale Group.)*

is again removed, and a piece of fine wire threaded through its tip transfers the specimen onto sterile gauze. The patient may feel discomfort or pressure when the needle is inserted and experience a brief, pulling sensation when the marrow is withdrawn. Unlike aspiration specimens, which are smeared, these samples contain structurally intact bone marrow. Microscopic examination can show what material its cells contain and how they are alike or different from one another. The bone may either be embedded intact in paraffin (a type of wax), or be decalcified (a process which takes place overnight) for a different type of staining and examination. Each type of preparation has certain advantages.

Preparation

A current history and physical are obtained from the patient, along with proper consent. The patient is generally placed in a prone position (lying face down) for preparation, and local anesthetic, with or without sedation, is administered.

Aftercare

After the needle is removed, the biopsy site will be covered with a clean, dry bandage. Pressure is applied to control bleeding. The patient's pulse, breathing, blood pressure, and temperature are monitored until they return to normal, and the patient may be instructed to remain in a supine position (lying face up) for half an hour before getting dressed.

The patient should be able to leave the clinic and resume normal activities immediately. Patients who have received a sedative often feel sleepy for the rest of the day; driving, cooking, and other activities that require clear thinking and quick reactions should therefore be avoided.

The biopsy site should be kept covered and dry for several hours. Walking or taking prescribed pain medications usually ease any discomfort felt at the biopsy site, and ice can be used to reduce swelling.

A doctor should be notified if the patient:

- Feels severe pain more than 24 hours after the procedure.
- Experiences persistent bleeding or notices more than a few drops of blood on the wound dressing.
- Has a temperature above 101°F (38.3°C). Inflammation and pus at the biopsy site and other signs of infection should also be reported to a doctor without delay.

KEY TERMS

Aspiration—A procedure to withdraw fluid from the body.

Connective tissue—Material that links one part of the body with another.

Fibrosis—A condition characterized by the presence of scar tissue or fiber-containing tissues that replace normal tissues.

Hematologist—A medical specialist who treats diseases and disorders of the blood and blood-forming organs.

Hematoma—Blood that collects under the skin and causes swelling.

Hemorrhage—Heavy bleeding.

Myeloma—A tumor that originates in bone marrow and usually spreads to more than one bone.

Nurse practitioner—A registered nurse who is qualified to perform some specialized duties.

QUESTIONS TO ASK THE DOCTOR

- What will this tell me about my condition?
- What should I do to prepare for this procedure?
- What are my chances of infection or other complications?
- What future care will I need?

Risks

Bleeding and discomfort often occur at the biopsy site. Infection and hematoma may also develop. In rare instances, the heart or a major blood vessel is pierced when marrow is extracted from the sternum during bone marrow biopsy. This can lead to severe hemorrhage.

Normal results

Healthy adult bone marrow contains yellow fat cells, connective tissue, and red marrow that produces blood. The bone marrow of a healthy infant is primarily red due to active production of red cells necessary for growth.

Abnormal results

Culture of bone marrow aspirate may yield information about an infectious agent. Microscopic examination of bone marrow can reveal granulomas, **myelofibrosis**, lymphomas, leukemias, or other cancers. Analyzing specimens can help doctors diagnose iron deficiency, vitamin B_{12}deficiency, and folate deficiency, as well as anemia.

Obesity can affect the ease with which a bone marrow biopsy can be done, and the results of either procedure can be affected if the patient has had **radiation therapy** at the biopsy site.

Maureen Haggerty

Bone marrow transplantation

Definition

The bone marrow—the sponge-like tissue found in the center of certain bones—contains stem cells that are the precursors of white blood cells, red blood cells, and platelets. These blood cells are vital for normal body functions, such as oxygen transport, defense against infection and disease, and clotting. Blood cells have a limited lifespan and are constantly being replaced; therefore, healthy stem cells are vital.

In association with certain diseases, stem cells may produce too many, too few, or otherwise abnormal blood cells. Also, medical treatments may destroy stem cells or alter blood cell production. The resultant blood cell abnormalities can be life threatening.

Bone marrow transplantation involves extracting bone marrow containing normal stem cells from a healthy donor, and transferring it to a recipient whose body cannot manufacture proper quantities of normal blood cells. The goal of the transplant is to rebuild the recipient's blood cells and immune system and hopefully cure the underlying ailment.

Purpose

A person's red blood cells, white blood cells, and platelets may be destroyed or may be abnormal due to disease. Also, certain medical therapies, particularly **chemotherapy** or **radiation therapy**, may destroy a person's stem cells. The consequence to a person's

health is severe. Under normal circumstances, red blood cells carry oxygen throughout the body and remove carbon dioxide from the body's tissues. White blood cells form the cornerstone of the body's immune system and defend it against infection. Platelets limit bleeding by enabling the blood to clot if a blood vessel is damaged.

A bone marrow transplant is used to rebuild the body's capacity to produce these blood cells and bring their numbers to normal levels. Illnesses that may be treated with a bone marrow transplant include both cancerous and noncancerous diseases.

Cancerous diseases may or may not specifically involve blood cells; but, cancer treatment can destroy the body's ability to manufacture new blood cells. Bone marrow transplantation may be used in conjunction with additional treatments, such as chemotherapy, for various types of leukemia, **Hodgkin's disease**, **lymphoma**, breast and **ovarian cancer**, and other cancers. Noncancerous diseases for which bone marrow transplantation can be a treatment option include aplastic anemia, sickle cell disease, thalassemia, and severe immunodeficiency.

Precautions

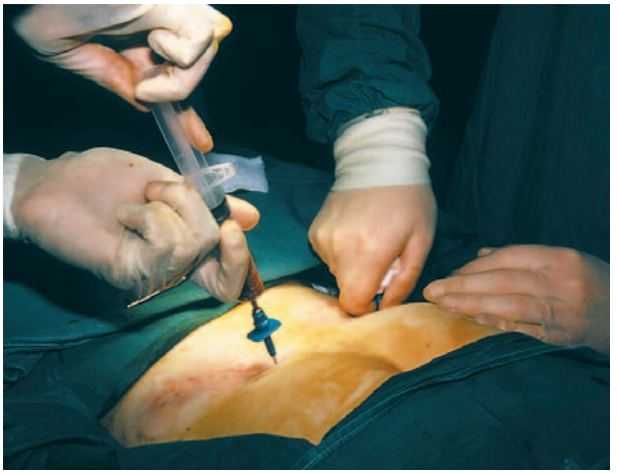
Bone marrow transplants are not for everyone. Transplants are accompanied by a risk of infection, transplant rejection by the recipient's immune system, and other complications. The procedure has a lower success rate the greater the recipient's age. Complications are exacerbated for people whose health is already seriously impaired as in late-stage cancers. Therefore, a person's age or state of health may prohibit use of a bone marrow transplant. The typical cut-off age for a transplant ranges from 40 to 55 years; however, a person's general health is usually the more important factor.

Even in the absence of complications, the transplant and associated treatments are hard on the recipient. Bone marrow transplants are debilitating. A person's ability to withstand the rigors of the transplant is a key consideration in deciding to use this treatment.

Description

Autologous and allogeneic transplants

Two important requirements for a bone marrow transplant are the donor and the recipient. Sometimes, the donor and the recipient may be the same person. This type of transplant is called an autologous transplant. It is typically used in cases in which a person's bone marrow is generally healthy but will be destroyed due to medical treatment for diseases such as **breast cancer** and Hodgkin's disease. Most bone marrow transplants are autologous. If a person's bone marrow is unsuitable for an autologous transplant, the bone marrow must be derived from another person in an allogeneic transplant.



Treatment of acute leukemia by bone marrow transplant. *(Photo Researchers, Inc. Reproduced by permission.)*

Allogeneic transplants are more complicated because of proteins called human lymphocyte antigens (HLA) that are on the surface of bone marrow cells. If the donor and the recipient have very dissimilar antigens, the recipient's immune system regards the donor's bone marrow cells as invaders and launches a destructive attack against them. Such an attack negates any benefits offered by the transplant.

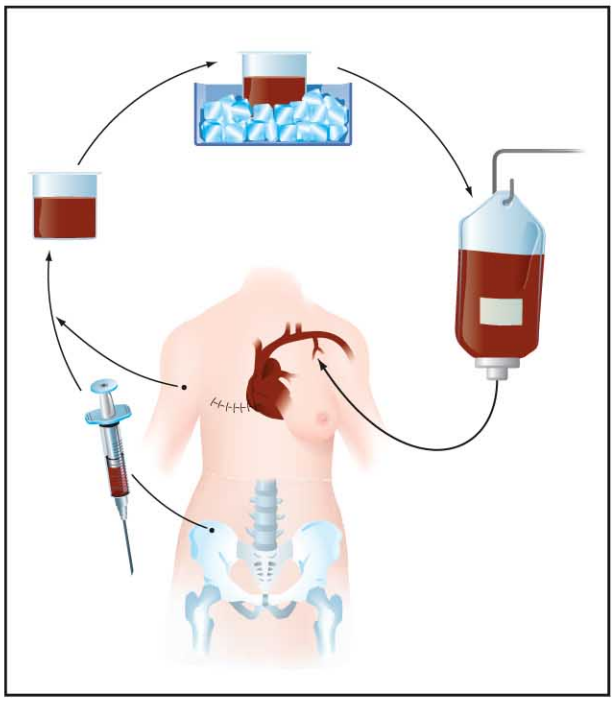
HLA matching

There are only five major HLA classes or types—designated HLA–A,–B, –C,–D, and class III—but much variation within the groupings. For example, HLA–A from one individual may be similar to, but not the same as, HLA–A in another individual; such a situation can render a transplant from one to the other impossible.

HLA matching is more likely if the donor and recipient are related, particularly if they are siblings; however, an unrelated donor may be a potential match. Only in rare cases is matching HLA types between two people not an issue: if the recipient has an identical twin. Identical twins carry the same genes; therefore, the same antigens. A bone marrow transplant between identical twins is called a syngeneic transplant.

Peripheral blood stem cell transplants

A relatively recent development in stem cell transplantation is the use of peripheral blood stem cells instead of cells from the bone marrow. Peripheral blood



In autologous bone marrow transplantation, stem cells are collected. Once the patient has undergone chemotherapy, the cells are replaced in the blood via an intravenous catheter. The cells return to the bone marrow and begin producing healthy new cells. *(Illustration by Argosy Publishing, Inc. Reproduced by permission of The Gale Group.)*

stem cells (PBSCs) are obtained from circulating blood rather than from bone marrow, but the amount of stem cells found in the peripheral blood is much smaller than the amount of stem cells found in the bone marrow. Peripheral blood stem cells can be used in either autologous or allogeneic transplants. The majority of PBSC transplants are autologous. However, recent clinical studies indicate that PBSCs are being used more frequently than bone marrow for allogeneic bone marrow transplantation.

The advantages of PBSC transplants when compared to bone marrow transplants are: in allogeneic transplantation, haematopoietic and immune recovery are faster with PBSCs. In autologous transplantation, the use of PBSCs can result in faster blood count recovery. Also, some medical conditions exist in which the recipient cannot accept bone marrow transplants, but can accept PBSC transplants. Some possible disadvantages to PBSC transplant versus bone marrow transplantation are: so much more fluid volume is necessary to collect enough PBSCs that, at the time that the new stem cells are infused into the recipient, the fluid can collect in the lungs. Also, the time commitment for the donor for a PBSC transplant is considerable. When the PBSCs are being collected, several outpatient sessions are needed and each session lasts approximately two–four hours.

The transplant procedure

BONE MARROW TRANSPLANTATION The bone marrow extraction, or harvest, is the same whether for an autologous or allogeneic transplant. Harvesting is done under general anesthesia (i.e., the donor sleeps through the procedure), and discomfort is usually minimal afterwards. Bone marrow is drawn from the iliac crest (the part of the hip bone to either side of the lower back) with a special needle and a syringe. Several punctures are usually necessary to collect the needed amount of bone marrow, approximately 1–2 quarts. (This amount is only a small percentage of the total bone marrow and is typically replaced within four weeks.) The donor remains at the hospital for 24–48 hours and can resume normal activities within a few days.

If the bone marrow is meant for an autologous transplant, it is stored at –112 to –320°F (–80 to –196°C) until it is needed. Bone marrow for an allogeneic transplant is sometimes treated to remove the donor's T cells (a type of white blood cell) or to remove ABO (blood type) antigens; otherwise, it is transplanted without modification.

The bone marrow is administered to the recipient via a catheter (a narrow, flexible tube) inserted into a large vein in the chest. From the bloodstream, it migrates to the cavities within the bones where bone marrow is normally stored. If the transplant is successful, the bone marrow begins to produce normal blood cells once it is in place, or engrafted.

PERIPHERAL BLOOD STEM CELL TRANSPLANTATION Before collection for a PBSC transplant, donors receive daily four injections of the drug G-CSF, or **filgrastim**. (Patients can give it to themselves at home if need be.) These pretreatments stimulate the body to release stem cells into the blood. After these pretreatments, the donors' experience is similar to that of a whole blood donor's experience— PBSC donors' blood is collected at a clinic or hospital as an outpatient procedure. The differences are that several sessions will be needed over days or weeks and the blood is collected in a process called apheresis. The blood travels from one arm into a blood cell separator that removes only the stem cells, and the rest of the blood is returned back to the donor, in the other arm. The cells are then frozen for later use.

The PBSCs are administered to the recipient using the same methods as those used in bone marrow transplantation. As stated, the amount of fluid with PBSCs infused into the recipient's body can be an issue.

KEY TERMS

ABO antigen—Protein molecules located on the surfaces of red blood cells that determine a person's blood type: A, B, or O.

AML—Acute myelogenous leukemia, also called acute myelocytic leukemia. Malignant disorder where myeloid blast cells accumulate in the marrow and bloodstream.

Allogeneic—Referring to bone marrow transplants between two different, genetically dissimilar people.

Anemia—Decreased red cell production which results in deficiency in oxygen-carrying capacity of the blood.

Antigen—A molecule that is capable of provoking an immune response.

Aplastic anemia—A disorder in which the body produces inadequate amounts of red blood cells and hemoglobin due to underdeveloped or missing bone marrow.

Autologous—Referring to bone marrow transplants in which recipients serve as their own donors.

Blank—If an individual has inherited same HLA antigen from both parents, the HLA typing is designated by the shared HLA antigen followed by a "blank"(–)

Blast cells—Blood cells in early stage of cellular development.

Blast crisis—Stage of chronic myelogenous leukemia where large quantities of immature cells are produced by the marrow and is not responsive to treatment.

Bone marrow—A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains stem cells, the precursors of platelets, red blood cells, and white blood cells.

Bone marrow transplant—Healthy marrow is infused into people who have had high-dose chemotherapy for one of the many forms of leukemias, immunodeficiencies, lymphomas, anemias, metabolic disorders, and sometimes solid tumors.

Chemotherapy—Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

Chronic myelogenous leukemia (CML)—Also called chronic myelocytic leukemia, malignant disorder that involves abnormal accumulation of white cells in the marrow and bloodstream.

Cytomegalovirus (CMV)—Virus that can cause pneumonia in post bone marrow transplant patients

Conditioning—Process of preparing patient to receive marrow donation, often through the use of chemotherapy and radiation therapy

Confirmatory typing—Repeat tissue typing to confirm the compatibility of the donor and patient before transplant

Donor—A healthy person who contributes bone marrow for transplantation.

Graft versus host disease—A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

Histocompatibility—The major histocompatibility determinants are the human leukocyte antigens (HLA) and characterize how well the patient and donor are matched.

HLA (human leuckocyte antigen)—A group of protein molecules located on bone marrow cells that can provoke an immune response. A donor's and a recipient's HLA types should match as closely as possible to prevent the recipient's immune system from attacking the donor's marrow as a foreign material that does not belong in the body.

Hodgkin's disease—A type of cancer involving the lymph nodes and potentially affecting nonlymphatic organs in the later stage.

Immunodeficiency—A disorder in which the immune system is ineffective or disabled either due to acquired or inherited disease.

Leukemia—A type of cancer that affects leukocytes, a particular type of white blood cell. A characteristic symptom is excessive production of immature or otherwise abnormal leukocytes.

Lymphoma—A type of cancer that affects lymph cells and tissues, including certain white blood cells (T cells and B cells), lymph nodes, bone marrow, and the spleen. Abnormal cells (lymphocyte/leukocyte) multiply uncontrollably.

Match—How similar the HLA typing, out of a possible six antigens, is between the donor and the recipient.

Mixed lymphocyte culture (MLC)—Test that measures level of reactivity between donor and recipient lymphocytes.

KEY TERMS (contd.)

Neuroblastoma—Solid tumor in children, may be treated by BMT.

Platelets—Fragments of a large precursor cell, a megakaryocyte found in the bone marrow. These fragments adhere to areas of blood vessel damage and release chemical signals that direct the formation of a blood clot.

Recipient—The person who receives the donated blood marrow.

Red blood cells—Cells that carry hemoglobin (the molecule that transports oxygen) and help remove wastes from tissues throughout the body.

Sickle cell disease—An inherited disorder characterized by a genetic flaw in hemoglobin production. (Hemoglobin is the substance within red blood cells that enables them to transport oxygen.) The hemoglobin that is produced has a kink in its structure that forces the red blood cells to take on a sickle shape, inhibiting their circulation and causing pain. This disorder primarily affects people of African descent.

Syngeneic—Referring to a bone marrow transplant from one identical twin to the other.

Thalassemia—A group of inherited disorders that affects hemoglobin production. (Hemoglobin is the substance within red blood cells that enables them to transport oxygen.) Because hemoglobin production is impaired, a person with this disorder may suffer mild to severe anemia. Certain types of thalassemia can be fatal.

White blood cells—A group of several cell types that occur in the bloodstream and are essential for a properly functioning immune system.

Costs

Bone marrow transplantation is an expensive procedure. (Bone marrow donors are volunteers and do not pay for any part of the procedure.) Insurance companies and health maintenance organizations (HMOs) may not cover the costs.

Preparation

A bone marrow transplant recipient can expect to spend 4–8 weeks in the hospital. In preparation for receiving the transplant, the recipient undergoes "conditioning"—a preparative regimen in which the bone marrow and abnormal cells are destroyed. Conditioning rids the body of diseased cells and makes room for the marrow to be transplanted. It typically involves chemotherapy and/or radiation treatment, depending on the disease being treated. Unfortunately, this treatment also destroys healthy cells and has many side effects such as extreme weakness, nausea, vomiting, and **diarrhea**. These side effects may continue for several weeks.

Aftercare

A two- to four-week waiting period follows the marrow transplant before its success can begin to be judged. The marrow recipient is kept in isolation during this time to minimize potential infections. The recipient also receives antibiotic medications and blood and platelet transfusions to help fight off infection and prevent excessive bleeding. Further side effects, such as **nausea and vomiting**, can be treated with other medications. Once blood counts are normal and the side effects of the transplant abate, the recipient is taken off **antibiotics** and usually no longer needs blood and platelet transfusions.

Following discharge from the hospital, the recipient is monitored through home visits by nurses or out-patient visits for up to a year. For the first several months out of the hospital, the recipient needs to be careful in avoiding potential infections. For example, contact with other people who may be ill should be avoided or kept to a minimum. Further blood transfusions and medications may be necessary, but barring complications, the recipient can return to normal activities about six to eight months after the transplant.

Risks

Bone marrow transplants are accompanied by serious and life-threatening risks. Furthermore, they are not always an absolute assurance of a cure for the underlying ailment; a disease may recur in the future. Approximately 30% of people receiving allogeneic transplants do not survive. Autologous transplants have a much better survival rate—nearly 90%—but are not appropriate for all types of ailments requiring a bone marrow transplant. Furthermore, they have a higher failure rate with certain diseases, specifically leukemia.

In the short term, there is the danger of **pneumonia** or other infectious disease, excessive bleeding, or liver

QUESTIONS TO ASK THE DOCTOR

- What is allogenic bone marrow transplantation (BMT)?
- What is syngenic bone marrow transplantation?
- What is autologous bone marrow transplantation?
- What is Graft-versus-Host disease (GVHD) and can it be prevented?
- What diseases are treated by BMT?
- What is HLA/histocompatibility matching?

disorder caused by blocked blood vessels. The transplant may be rejected by the recipient's immune system, or the donor bone marrow may launch an immune-mediated attack against the recipient's tissues. This complication is called acute graft-versus-host disease, and it can be a life-threatening condition. Characteristic signs of the disease include **fever**, rash, diarrhea, liver problems, and a compromised immune system.

Approximately 25–50% of bone marrow transplant recipients develop long-term complications. Chronic graft-versus-host disease symptoms include skin changes such as dryness, altered pigmentation, and thickening; abnormal liver function tests; dry mouth and eyes; infections; and **weight loss**. Other long-term complications include cataracts (due to radiation treatment), abnormal lung function, hormonal abnormalities resulting in reduced growth or hypothyroidism, secondary cancers, and infertility.

Normal results

In a successful bone marrow transplant, the donor's marrow migrates to the cavities in the recipient's bones and produces normal numbers of healthy blood cells. Bone marrow transplants can extend a person's life, improve quality of life, and may aid in curing the underlying ailment.

Resources

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Nuzhat, Iqbal, Donna Salzman, Audrey J. Lazenby, et al. "Diagnosis of Gastrointestinal Graft-Versus-Host Disease." *The American Journal of Gastroenterology* 95 (November 2000): 3034- 3038.

ORGANIZATIONS

American Society for Blood and Marrow Transplantation (ASBMT). 85 W. Algonquin Road, Suite 550 Arlington Heights, IL 60005. (847) 427-0224. mail@asbmt.org. Founded in 1990, a national professional association that promotes advancement of the field of blood and bone marrow transplantation in clinical practice and research.

Blood & Marrow Transplant Newsletter (Formerly BMT Newsletter). 2900 Skokie Valley Road, Suite B, Highland Park, IL 60035 (847) 433-3313. 1-888-597-7674. help@bmtinfonet.org. <http://www2.bmtnews.org>. Blood & Marrow Transplant Newsletter is a not-for-profit organization that provides publications and support services to bone marrow, peripheral blood stem cell, and cord blood transplant patients and survivors.

BMT Information . <http://www.bmtinfo.org/>. Web site, sponsored by a variety of other bone marrow transplant organizations, lists basic information and resources about bone marrow transplants.

Health Resources and Services Administration. 5600 Fishers Lane, Rm. 14-45, Rockville, MD 20857, 301-443-3376, comments@hrsa.gov. <http://www.hrsa.gov>. HRSA manages contracts for the Organ Procurement and Transplantation Network, Scientific Registry of Transplant Recipients and National Marrow Donor Program and provides public education and technical assistance to increase donation. HRSA also monitors the performance of the nation's transplant centers and provides potential transplant recipients with survival rates and other vital information.

International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry N. America. Health Policy Institute, Medical College of Wisconsin, 8701 Watertown Plank Road, P.O. Box 26509, Milwaukee, WI 53226 USA, 414-456-8325, ibmtr@mcw.edu. Voluntary organizations of more than 400 institutions in 47 countries that submit data on their allogeneic and autologous blood and marrow transplant recipients to the IBMTR/ABMTR Statistical Center at the Medical College of Wisconsin in Milwaukee.

Leukemia & Lymphoma Society, Inc. 1311 Mamaroneck Avenue White Plains, NY 10605, 914-949-5213 <http://www.leukemia-lymphoma.org/>. National voluntary health agency dedicated to curing leukemia, lymphoma, Hodgkin's disease and myeloma, and to improving the quality of life of patients and their families.

National Marrow Donor Program. Suite 500, 3001 Broadway Street Northeast, Minneapolis, MN 55413-1753. (800) MARROW-2. <http://www.marrow.org>. Founded in 1986, The National Marrow Donor Program (NMDP) is a non-profit international leader in the facilitation of unrelated marrow and blood stem cell transplantation.

National Organ and Tissue Donation Initiative. <http://www.organdonor.gov/> Created by Health Resources and

Services Administration (HRSA) Department of Health and Human Services (DHHS) <http://www.os.dhhs.gov/>. Provides information and resources on organ donation and transplantation issues.

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Bone pain

Description

Bone pain represents one of the most debilitating side effects of the metastases (distant spread) of many cancers such as breast, prostate, lung, and **multiple myeloma** (myelomatosis). Severe bone pain is frequent, reported by greater than 65% of patients suffering with bone metastases. The most common sites affected include the pelvis, femur, skull, and vertebra. The patient often describes the pain as dull and aching, localized at the site affected; however, some patients experience short, shooting pain that radiates out from the torso to the extremities. Movement typically aggravates the pain. Bone pain can signal disease progression, a new infection, or a complication from treatment. Pain is a reliable early indicator of complications from metastases — osteoporosis, **hypercalcemia**, fractures, and **spinal cord compression**. These conditions not only adversely affect the patient's quality of life, but in some cases may create such a decline that death results not from the cancer, but from bone- and skeletal-related complications. When a patient complains of bone pain, it require confirmation, usually by imaging. Plain-film radiography may detect typical lesions, but may not be sensitive enough to detect certain complications. In these cases, radionuclide scintigraphy and **magnetic resonance imaging** (MRI) are the preferred diagnostic tools.

Causes

Bone pain may be the result of direct tumor involvement. Pain is produced when the tumor pushes against or enters the bone. The tumor may compress surrounding blood vessels, nerves, and soft tissue, or may activate nociceptors (pain receptors) located at the site. Pain also may result from tissue compression caused by fibrosis (a condition caused by an increase in tissue) after the patient has undergone **radiation therapy**. A major source of bone pain in the cancer patient is pathologic fracture and osteoclast-induced bone resorption by the tumor. This condition promotes bone loss and, at the same time, provides growth factors for the tumor to increase in size.

KEY TERMS

Calcitonin—A hormone produced by the thyroid that causes a reduction of calcium ions in the blood.

Cognitive distraction and reframing—Techniques to teach the patient to focus on things not associated with pain.

Hypercalcemia—The presence of abnormally high concentrations of calcium compounds in the bloodstream.

Magnetic resonance imaging (MRI)—A diagnostic technique that makes images of internal structures of the body, often superior to a normal x ray.

Metastases—Cancer that starts from cancer cells that originate in a different location in the body.

Multiple myeloma—Multiplying plasma cells that often replace all other cell types found in the bone marrow and frequently cause the loss of the bone cortex.

Nociceptors—Peripheral pain receptors that are sensitive to movement, extreme heat and cold, and chemical stimuli.

Opioid—Any morphine-like compound producing bodily effects that may include relief from severe pain, respiratory depression, or sedation.

Osteoclast—Cells responsible for the breakdown of bone tissue.

Radionuclide scintigraphy—The process of injecting a radionuclide to capture an image of a particular area of the body for diagnostic purposes.

Radiopharmaceuticals—Compounds used as radiation sources for radiotherapy and for diagnostic procedures.

Treatments

There are several options for pain management for bone metastases. The primary treatment for the majority of patients is external beam radiation therapy. These treatments provide excellent pain relief. Localized radiation treatments target specific sites for pain relief, promote healing, and help prevent fractures. Spinal cord compression from vertebral collapse requires immediate and localized radiation therapy, possibly in conjunction with surgical intervention to prevent paralysis or loss of life. Wide-field radiation therapy treats multiple disease sites and is appropriate for more diffuse bone pain. One half of the body receives radiation in a single treatment. Studies report relief of bone pain in 55%–100% of

patients. A 2003 study reported that external beam radiation therapy treatments provided significant pain relief for two-thirds of patients with bone mestastases from breast and prostate cancer.

Analgesics (pain relievers) are typically given in conjunction with radiotherapy. Severity of the bone pain and general health of the patient will determine the prescribed medication. The medications prescribed range from over-the-counter pain medicine to **opioids** for extreme bone pain management.

Radiopharmaceuticals may be an effective choice for bone pain management. Iodine-131 is used in the treatment of multiple bone metastases from **thyroid cancer**. Phosphorus-32 orthophosphate has a success rate of about 80% in bone pain management in patients suffering with breast and **prostate cancer**. Strontium-89 provides partial or complete pain relief in approximately 65% of patients. Other radiopharmaceuticals are being tested internationally but have not yet received FDA approval for use in the United States. In treatments for bone resorption-induced pain, a group of chemical agents, known as **bisphosphonates** and **calcitonin**, acts to strongly block the bone resorption process. These agents are used in the management of hypercalcemia and have the added effect of reducing the prescribed amount of analgesics and shortening the duration of bone pain.

Alternative and complementary therapies

Comprehensive management of bone pain includes non-clinical choices. Patients should be encouraged to participate in complementary therapies, and some patients may choose to investigate more alternative therapies. More conventional complementary therapies may include relaxation and imagery therapy, cognitive distraction and reframing, support group and pastoral counseling, skin stimulation, biofeedback, nerve blocks, immobilization and stabilization techniques, and surgical intervention. Less well-defined alternative therapies may include acupuncture, body massage with pressure and vibration techniques, hypnosis, menthol preparations, and holistic or herbal medical practices. No conclusive data exist on the effectiveness of these therapies used alone; however, in conjunction with conventional methods of bone pain management, they do not appear to hinder therapy and may provide the patient with increased goodwill and a positive outlook.

Resources

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Bone metastasis *see* **Metastasis**

Bone scan *see* **Nuclear medicine scans**

Bone survey

Definition

A bone survey is an **x ray** to check the health and status of a person's bones. It is an important tool for diagnosing the presence of **multiple myeloma** lesions in bone.

Purpose

The bone survey is the standard method for determining if there is bone involvement in multiple myeloma. Multiple myeloma lesions may not show up in other bone studies. However, if the lesions are present, they are likely to appear on a bone survey, making this an important diagnostic tool.

In patients who have been treated for multiple myeloma, bone surveys should be repeated to see if the disease has responded to treatment, or if it has progressed further. While the repeated bone survey may show that bone healing has occurred, this is not usually the case. Only 30% of patients whose multiple myeloma is responding to treatment show an improvement on their bone surveys. Multiple myeloma patients whose disease is progressing, or who have new areas of **bone pain**, can benefit from repeat bone surveys because this procedure can locate sites of potential fractures that may then be prevented by radiation or surgery.

Precautions

The dose of radiation in diagnostic x rays is very small, and this procedure is considered relatively safe. However, x rays are generally not advised for pregnant women. These women should inform their physician or the x-ray technician of their pregnancy (or suspected pregnancy) prior to the procedure.

Description

A bone survey in people with multiple myeloma includes x rays of the skull, spine, pelvis, and long bones

KEY TERMS

Radiologic procedure—A medical procedure, such as an x ray, that uses radiation or other sources to create images useful in diagnosis.

Radiologist—A medical doctor who specializes in interpreting radiologic (imaging) studies. Imaging studies include x ray, computed tomography (CT), and magnetic resonance imaging (MRI).

QUESTIONS TO ASK THE DOCTOR

- How long will the bone survey take?
- Where will the procedure be done?
- What is the risk from radiation?
- Who will examine the x rays?
- When will I get the results?
- If the results are abnormal, what treatment will be given?

of the legs and arms because the disease may spread to these particular areas. The procedure may be done in the radiology department of a hospital (for inpatients or outpatients) or in an imaging facility.

Patients may be given a hospital gown and asked to remove clothing that could interfere with the image, such as buttons or snaps. A lead shield for protection from radiation may be placed over the parts of the body that are not undergoing an x ray.

An x ray creates a two-dimensional (flat) image shown on film. Since the human body is three-dimensional, at least two different angles of the same area will be x-rayed. The radiology technician helps the patient achieve the proper position. Most imaging centers have special tables that help position the patient.

When the patient is properly positioned, the technician will leave the room to activate the x-ray machine. It is important that the patient remain completely still while the x ray is being taken. The x ray does not cause any pain or other sensation, and gives off no smell, sound, or taste, although it is penetrating the body. The patient may hear a sound, but this is the equipment and not the x ray itself.

The x ray creates shadows on film, and the film is viewed by a physician (radiologist) who specializes in **imaging studies**. The film will have contrasts that appear as varying shades of gray.

Preparation

Because the procedure in non-invasive, no specific preparation is necessary.

Aftercare

Bone surveys do not require any aftercare.

Risks

While radiation in high doses may present a cancer risk, the dosage for diagnostic purposes is very low. New technology has increased the safety of radiologic procedures. As in any procedure, the risk must be weighed against the benefit. In patients with multiple myeloma, the bone survey is needed to determine bone involvement, which could then dictate treatment. Pregnant women generally do not receive x rays, and should discuss this with their physician.

Normal results

Bone structure that is free of disease, fracture, or other problem areas is a normal result.

Abnormal results

Areas where multiple myeloma is present show up as destructive bone lesions. Parts of the bone may appear moth-eaten, and fractures may be present.

Resources

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Bortezomib

Definition

Bortezomib is an man-made antineoplastic drug used to treat **multiple myeloma**.

Purpose

Bortezomib is used to treat individuals with multiple **myeloma** that has continued to grow and spread after being treated with least two other types of therapy. Standard treatments for multiple myeloma include a combination of steroid drugs, **chemotherapy**, and stem cell transplantation.

Multiple myeloma is the second most common blood cancer in the United States, with about 14,600 new cases diagnosed each year. It arises in the plasma cells of the bone marrow and causes multiple tumors. Plasma cells, sometimes called myeloma cells, are part of the body's immune system. When they become cancerous, they multiply uncontrollably and produce abnormal proteins that interfere with the growth and functions of normal cells. The also can spread to other parts of the body.

Description

Bortezomib is a type of drug called a protease inhibitor. It sold in the United States under the brand name Velcade by Millennium Pharmaceuticals. It was approved for use by the United States Food and Drug Administration (FDA) in May 2003. Generic substitutes are not available.

Proteasome is an enzyme complex that plays a role in many metabolic processes of the cell related to cell growth. Bortezomib blocks the production of proteasome. By doing this, it slows cell growth and can cause the cells to die. Although bortezomib also affects healthy cells, it has a much greater effect on cancer cells, because they are rapidly so growing. As a result, tumor growth can be slowed.

Recommended dosage

Bortezomib is given in a hospital or clinic by injection into a vein. It is a white powder that comes in a single-dose vial to which saline is added just before use. The therapeutic administration cycle is three weeks. This cycle can be repeated up to eight times. Individuals are given a dose based on body size on days one, four, eight and 11. This is followed by a 10-day rest period, after which the cycle is repeated. Regular monitoring of blood count is done throughout treatment. The dose may be adjusted based on laboratory results and side effects, but the timing of administration remains the same.

KEY TERMS

Antineoplastic—A drug that is used against new, rapidly growing cancer cells.

Enzyme—A complex protien produced in a cell that mediates a chemical reaction.

Peripheral neuropathy—A set of symptoms of a nervous disorder in the extremities (hands and feet) that includes pain, numbness, tingling, and burning.

Saline—Sterile salt water that approximates the concentration of salts in the blood.

Tumor lysis syndrome—A condition that occurs after chemotherapy in which phosphates, potassium, and uric acid rise to abnormally high levels in the blood and calcium falls to abnormally low levels. This is thought to be the result of products released by dying cancer cells.

Precautions

Bortezomib should not be given to individuals who have shown hypersensitivity to bortezomib, boron, or mannitol. Individuals who have numbness, pain, burning, or tingling their hands and feet (peripheral **neuropathy**) may not be good candidates to receive this drug, because bortezomib causes or enhances these symptoms. If symptoms become intense enough, the therapy must be stopped. Bortezomib also causes or enhances low blood pressure and can worsen congestive heart failure. Individuals with these conditions may need dosage adjustment. Individuals with liver or kidney disease may also need to have their dosage reduced.

Bortezomib can cause harm to the developing fetus and should not be used by pregnant women. Women should use birth control for 12 months after receiving this therapy. It has not been established whether this therapy is safe to use in breastfeeding women. A pediatric dose has not been established.

Side effects

Side effects are many and varied. The most common include:

- peripheral neuropathy; tingling, pain and loss of sensation or numbness in the hands and feet
- low blood pressure (hypotension) and dizziness, especially when going from lying or sitting to standing
- nausea, vomiting, **diarrhea**, dehydration severe enough to require medication and/or fluid and electrolyte replacement

- frequent bleeding; decrease in the ability of blood to clot (**thrombocytopenia**) caused by death of blood platelets and low platelet count
- tumor lysis syndrome that causes chemical imbalances in the blood
- fever
- increased susceptibility to infection
- weakness, **fatigue**, fainting, light-headedness, blurred vision; individuals should avoid driving and operating machinery.

Other side effects that may occur include:

- anxiety, agitation, or insomnia
- muscle and joint aches or cramps
- cough
- rash
- headache
- decreased appetite

Interactions

It is important to tell the physician about all prescription medications, over-the-counter medications, and herbal or alternative remedies that are being taken before treatment with bortezomib is begun. Although formal drug interaction studies have not been completed, a number of drugs may interact with bortezomib, especially those that lower blood pressure or cause symptoms of peripheral neuropathy. These include:

- amiodarone (Cordarone, Pacerone)
- blood thinners (**warfarin**, Coumadin, Plavix)
- bosentan (Tracleer)
- carbamazepine
- cimetidine (Tagamet)
- clarithromycin (Biaxin)
- erythromycin
- fluoxetine (Prozac, Sarafem)
- fluvoxamine (Luvox)
- nefazodone
- phenytoin (Dilantin)
- rifabutin (Mycobutin)
- rifampin (Rifadin, Rimactane)
- St. John's wort (herbal treatment)
- medications to treat fungal infections
- some diabetes medications

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Bowen's disease

Definition

Bowen's disease is a superficial precancerous squamous cell cancer, slow-growing (i.e. has not started spreading) skin malignancy. It is named for John Templeton Bowen (1857–1941), an American dermatologist. Bowen's disease is also called precancerous dermatosis.

Description

Red-brown, scaly or crusty patch on the skin that resembles psoriasis, dermatitis or eczema that can occur on any part of the body.

Demographics

Bowen's disease affects both males and females. Women are affected in the genital area three times as often as men. The disease can occur at any age, but is rare in children.

Causes and symptoms

The exact cause of Bowen's disease is unknown. Like many forms of cancer, long-term sun exposure may be a cause. The skin usually indicates sun damage, such as wrinkling, changes in pigmentation, and loss of elasticity. Ingestion of arsenic has been associated with cases of Bowen's disease found in skin areas unexposed to light or mucous membranes. Human papillomavirus 16 DNA is found repeatedly in Bowen's disease lesions, which suggests that this virus might be a cause. The role of heredity is not well understood. There are cases of Bowen's disease for which a cause cannot be determined.

Symptoms

The symptoms of Bowen's disease include:

- plaque located on or within the skin (intraepidermal)
- open sore that bleeds and crusts and persists for weeks
- wart-like growth that crusts and occasionally bleeds
- persistent, scaly red patch with irregular borders that sometimes crusts or bleeds
- pinkish or brownish raised areas of skin

Diagnosis

Bowen's disease can be confused with such other common skin disorders as psoriasis or types of dermatitis. **Paget's disease of the breast** and malignant **melanoma** are other types of cancer which may be confused

for Bowen's disease. A medical history, physical examination, and **biopsy** establish the diagnosis.

Clinical staging, treatments, and prognosis

Treatment usually involves surgical removal of the lesion. Curettage and cautery methods,which include carbon dioxide lasers, liquid nitrogen, and topical fluorouracil (5-fluorouracil, FU) compose the most efficient treatment for management of small solitary lesions.

There can be difficulties with the liquid nitrogen, 5-FU (Efudex, fluoroplex), scraping and burning because Bowen's lesions can hide deep in pores, and cells may extend into the surrounding area where the lesion is visible.

Newer treatments for Bowen's disease include acitretin (Soriatane), an oral medication originally developed to treat psoriasis; and imiquimod (Aldara), an immune response modifier available as a 5% topical cream. Imiquimod has been reported to give good results in treating Bowen's disease of the penis as well as large facial lesions.

Clinical trials

Dr. Colin Morton and colleagues at the Western Infirmary in the UK have been developing a photodynamic therapy using topical 5-aminolaevulinic acid(5-ALA).

Dr. Lee and colleagues at the University College of Medicine in Korea have been developing a specially designed radioactive skin patch.

Prevention

As with most skin cancers, prolonged exposure to the sun can increase the risk of developing the disease.

Special concerns

All treatment options for Bowen's disease have a recurrence rate of 5–10%, and no treatment modality seems superior for all clinical situations.

Resources

BOOKS

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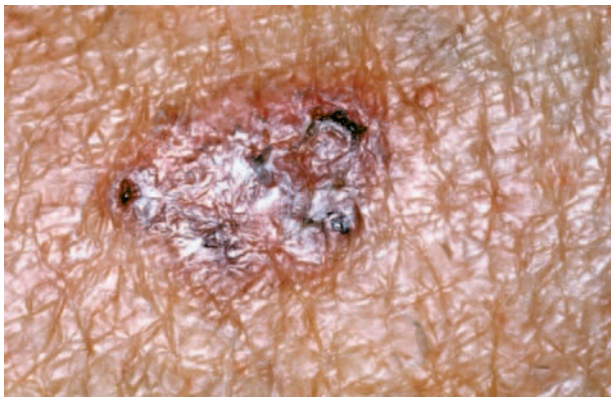

Close-up of a dark, bruise-like lesion on the leg of an elderly woman, caused by Bowen's disease. *(Copyright Dr. P. Marazzi, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

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KEY TERMS

Cancer—General term for abnormally growing (malignant) cells.

Dermatitis—Inflammation of the skin that may be due to an allergic reaction.

Melanoma—Abnormal growth in melanin cells which are most commonly found in the skin or in the eye.

Paget's disease of the breast—Cancer of breast nipples that occurs in both men and women. Paget's is characterized by oozy and crusty skin inflammation (dermatitis).

Precancerous dermatosis—Another name for Bowen's disease.

Psoriasis—Common inherited condition that is characterized by reddish, silvery-scaled maculo-papules, predominantly on the elbows, knees, scalp, and trunk.

Squamous cell carcinoma—Type of skin cancer

QUESTIONS TO ASK THE DOCTOR

- How do I know I have Bowen's disease rather than psoriasis, Paget's disease, dermatitis or another skin cancer?
- Is surgical removal of the affected skin area the best treatment?
- What other treatments for Bowen's disease are available other than surgical removal?

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Laura Ruth, Ph.D.
Rebecca J. Frey, PhD

Brain and central nervous system tumors

Definition

Like all other parts of the body, the brain and central nervous system are made up of cells that ordinarily grow and divide to create new cells as needed. This is usually an orderly process; but when cells lose their ability to grow normally or to die off naturally, they divide too often and produce tumors that are made up of these extra cells.

Description

The brain and spinal cord together comprise what is known as the central nervous system (CNS). Like all tumors in the body, CNS tumors are either benign or

malignant. Benign tumors are called non-cancerous because they have precise borders, are not invasive, and the cells that make up the growth are similar to other normal cells and grow relatively slowly. However, benign CNS tumors can press on a specific region of the spinal cord or brain and, thereby, cause symptoms. However, when such a benign tumor develops in an area that interferes with essential nervous system functioning, it is treated as malignant.

Malignant, or cancerous, tumors of the central nervous system are likely to be fast-growing, are invasive into surrounding healthy tissue, and the cells are very different from normal cells. These tumors can create a life-threatening situation by stopping vital functions of the brain. Some cancerous CNS tumors do not put out roots nor do they grow rapidly. These tumors are described as being encapsulated.

Another way that brain and central nervous system tumors are classified is by site of origin. Those that actually develop in the brain or spinal cord are called primary CNS tumors. **Metastasis** to the brain or spinal cord is, for the most part, a one-way street, meaning these tumors almost never metastasize to other areas in the body. The tumors that develop elsewhere in the body and metastasize, or spread, to the central nervous system are considered to be secondary CNS tumors. Such metastatic cells do not resemble other CNS cells. Instead, they have the same appearance as the cancer cells at the original cancer site elsewhere in the body.

Frequently observed signs of a brain tumor are the following:

- severe headaches
- an ataxic, or stumbling, gait
- **nausea and vomiting**
- lack of coordination
- unusual drowsiness
- weakness or loss of feelings in the arms and legs
- changes in personality or memory
- changes in speech
- changes in vision or abnormal eye movements
- seizures

Approximately 1 1/2% of all diagnosed cancers are CNS cancers, and they account for about 2 1/2% of all cancer deaths. The American Cancer Society (ACS) estimates that in 2001 17,200 malignant tumors of the brain or spinal cord will be diagnosed in adults and children in the United States. Of those people diagnosed, ACS projects that 13,100 will die from malignant CNS tumors.

Brain and Central nervous system tumors

Gliomas	Non-glial Tumors
Astrocytomas	Medulloblastomas
Brain stem gliomas	Meningiomas
Ependymomas	Schwannomas
Oligodendrogliomas	Craniopharyngiomas
	Germinomas
	Pineal region tumors

Typically, diagnosis of CNS tumor is made by a physician who does a complete physical examination, including a family history and neurological examination. Computerized tomography (CT) scans, **magnetic resonance imaging** (MRI) scans, skull x rays, brain scans, angiograms, or myelograms are among the means of visualizing the brain or spinal cord to search for tumors.

General categories of treatment methods for CNS tumors include surgery, **radiation therapy**, and **chemotherapy**, with surgery being the single most commonly used therapy. Steroids are usually given prior to treatment to decrease swelling, and anti-convulsant drugs may be given to prevent seizures.

Types of cancers

Primary brain tumors are also classified by their site of origin. Gliomas, occurring in the glial, or supportive tissues around the brain, are the most common. Gliomas are further broken down into the following variations:

- **Astrocytomas** are named for the star-shaped, small cells that they are comprised of. Children may develop these in their brain stem, cerebrum, or cerebellum, while adults commonly develop them in the cerebrum.
- Brain-stem gliomas are usually astrocytomas that originate in the bottom, stem-like portion of the brain. Because this area controls many essential bodily functions, such tumors often cannot be removed.
- **Ependymomas** occur in the linings of the four brain ventricles, or chambers, or along the spinal cord. These are more common in children.
- **Oligodendrogliomas** are very rare and, when seen, are usually found in middle-aged adults. They grow slowly and ordinarily do not invade surrounding brain or spinal cord tissue. They originate in the cells responsible for the manufacture of myelin, a fatty covering for nerve tissue.

Other CNS tumors do not originate in glial tissue. Among these are:

- **Medulloblastomas**, tumors of the cerebellum, are most common in male children. Studies have shown

KEY TERMS

Angiogram—A diagnostic test that makes it possible for blood vessels to be seen on film by filling them with a contrast substance or dye that appears on x rays.

Anti-convulsant drugs—A group of medications used in the treatment of seizures.

Brain scan—A general term that can include CT scans, MRIs, seldom-used radionuclide scanning (use of radioactive isotopes), or ultrasounds.

Computerized tomography (CT) scan—The combined use of a computer and x rays that are passed through the body to produce clear, cross-sectional images.

Magnetic resonance imaging (MRI)—An imaging technique that produces good cross-sectional images without x rays or other radiation sources.

Myelogram—X-ray examination of the spinal cord after injection of a contrast substance or dye that shows up on x rays.

Neurological exam—A physical examination that focuses on the patient's nerves, reflexes, motor and sensory functions, and muscle strength and tone.

Seizures—Sudden, uncontrolled electrical activity in the brain resulting in characteristic twitching, or spastic, movements that may be accompanied by loss of consciousness.

Steroids—A group of drugs that are similar to the hormones produced by the cortex of the adrenal gland.

Ventricles of the brain—The four fluid-filled chambers, or cavities, found in the two cerebral hemispheres of the brain, at the center of the brain, and between the brain stem and cerebellum, and linked by channels, or ducts, allowing cerebral fluid to circulate through them.

these to originate in primitive nerve cells that normally would have disappeared soon after birth.

- **Meningiomas** are usually benign. They develop in the meninges, or brain linings, and grow very slowly. Because of this slow growth, they may go undetected for years. Meningiomas are more common in women between the ages of 30 and 50.
- Schwannomas are also benign tumors, specific to the myelin-producing cells (Schwann cells) for the acoustic, or hearing, nerve. These, too, are more common in women than men.
- **Craniopharyngiomas** are usually benign, but because of their location near the pituitary gland and hypothalmus, they can easily affect vital functions and are therefore treated as if malignant. They occur more frequently in children and teenagers.
- Germinomas, or **germ cell tumors**, develop from primitive sex cells called germ cells.
- Pineal-region tumors originate in the area near the pineal gland, a small central brain gland that secretes melatonin, a brain chemical. These can be either fast-growing pineoblastoma, or slow-growing pineocytoma.

Resources

ORGANIZATIONS

The American Cancer Society's Resource Center for Brain/Central Nervous System Tumors in Children. (800) ACS-2345.

Cancer Care, Inc. (800) 813-4673. <http://www.cancercare.org>.

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Joan Schonbeck, R.N.

Brain metastasis *see* **Metastasis**

BRCA 1 & 2

Definition

BRCA 1 and BRCA 2 are genes that encode for proteins that help prevent breast and ovarian cancers.

Description

Family histories of breast/ovarian cancers

Breast cancer is the second most commonly diagnosed cancer among women and the second leading cause of cancer death in women. An estimated 217,400 new breast cancer cases were diagnosed in the United States in 2004 and about 40,600 women died of breast cancer. About 5–10% of women with breast cancer have an inherited susceptibility. After gender and age, a family history of breast or **ovarian cancer** is the single best predictor of the likelihood that a woman will develop these cancers.

Family histories that suggest a hereditary predisposition for breast and ovarian cancer include:

- multiple affected family members, particularly a mother, sister, or daughter

- cancers occurring 5–15 years earlier than sporadic cancers (those not associated with a genetic risk)
- two or more primary cancers in a single individual, such as breast and ovarian cancers or bilateral breast cancer (separate cancers in each breast)
- male breast cancer
- other multiple cancers in the family, especially **prostate cancer**
- an Ashkenazi (eastern and central European) Jewish background.

BRCA gene alterations

BRCA stands for BReast CAncer or breast cancer susceptibility. After a long search for changes in DNA sequences that were common in breast-cancer-prone families, particularly Ashkenazi Jews, BRCA 1 was discovered in 1994 and BRCA 2 in 1995. Inherited alterations (mutations) in the DNA sequences of these genes account for 5–10% of all breast cancers.

BRCAs are inherited as autosomal dominant genes. This means that an altered BRCA gene can be passed from either a mother or a father to a son or a daughter. Humans have 23 pairs of chromosomes that carry genes. One member of each chromosome pair is inherited from the father and the other member of the pair is inherited from the mother, so that a person has two copies of each gene. If either parent has an altered BRCA, their children each have a 50% chance of inheriting the altered BRCA. Because the altered BRCA is dominant over the normal gene inherited from the other parent, a child who inherits one altered BRCA is at an increased risk for breast and/or ovarian cancer. Males with an altered BRCA gene, especially BRCA 2, are at increased risk for breast and prostate cancers.

Excepting Ashkenazi Jews, the likelihood of a BRCA mutation is:

- 0.5% in the general population
- 2% in women with breast cancer
- 9% in women under 40 with breast cancer
- 5% in men with breast cancer
- 10% in women with ovarian cancer.

The likelihood of a BRCA mutation in Ashkenazi Jews is:

- 2.5% in the general population
- 10% in women with breast cancer
- 30–35% in women under 40 with breast cancer
- 19% in men with breast cancer
- 36–41% in women with ovarian or primary peritoneal or pelvic cancers.

Among Ashkenazi Jews, 1% have an alteration called 185delAG in BRCA 1; 0.1% have a mutation called 5382insC in BRCA 1; and 1.4% have a mutation called 6174delT in BRCA 2. Each of these three mutations carries a similar breast cancer risk. Various other ethnic groups, including Norwegians, Dutch, and Icelanders, have different specific BRCA mutations.

Although more than 2,000 mutations and DNA sequence variations have been found in BRCAs, most of them do not increase an individual's risk of developing cancer. However 0.1%–0.6% of the general population may carry a potentially damaging BRCA 1 mutation.

Not everyone with an altered BRCA gene will develop cancer. An altered BRCA increases a woman's risk of developing breast cancer during her lifetime from 13.2% to 36–85%. In the general population most breast cancers occur in post-menopausal women over age 50. Women with BRCA mutations most often are diagnosed with breast cancer in their 40s. An altered BRCA increases a woman's lifetime risk of developing ovarian cancer from 1.7% to 16–60%. Women with a BRCA 1 mutation have about a 40% chance of developing ovarian cancer by age 70. Women with a BRCA 2 mutation have about a 20% risk of developing ovarian cancer by age 70. BRCA 2 mutations also double a man's risk for prostate cancer.

Not all breast or ovarian cancers in cancer-prone family are due to BRCA mutations. Mutations in BRCA 1 account for breast or ovarian cancers in 45% of families with a history of breast cancer and up to 90% in families with a history of both breast and ovarian cancers. BRCA 2 mutations account for breast cancer in about 35% of families with a history of breast cancer.

BRCA mutations also appear to be involved in fallopian tube cancers and in peritoneal cancers. Cancer of the peritoneum that surrounds the organs of the pelvis is similar to ovarian cancer.

BRCA 1-related breast cancer appears to be more aggressive than other types of breast cancer and has a poorer prognosis. Most BRCA 1-related ovarian cancers also are of a particular invasive type.

BRCAs are believed to code for tumor suppressor proteins that interact with one another. They are thought to be involved in repairing DNA following damage caused by radiation or other factors that might otherwise lead to cancer. BRCA proteins are very large and deleterious mutations in their genes usually result in a shortened, nonfunctional, or missing protein.

Genetic testing

Genetic testing for BRCA mutations that increase the risk of breast and ovarian cancers have been available since 1996; as of 2004 between 26% and 78% of at-risk women had chosen to be tested. Genetic counseling by a trained professional is a very important part of making the decision to be tested.

Results

For BRCA testing blood is drawn at a laboratory, doctor's office, clinic, or hospital and sent to a laboratory. The results may not be available for several weeks or months. Many laboratories offer screening for specific BRCA mutations that occur in certain families or ethnic groups. Although technically much simpler to perform, these tests may not detect other potentially significant BRCA mutations.

It often is best to first test for a BRCA mutation in a family member who has breast or ovarian cancer. If that person has an altered BRCA gene, it becomes a known mutation and other family members can be tested for that specific mutation. A positive test for that mutation indicates that the person is at an increased risk for cancer. A negative test for that mutation—called a true negative—indicates that the person is unlikely to have an increased risk for cancer.

If there is no known BRCA mutation to screen for, a negative test can be a false negative because the test may have missed the mutation. An ambiguous or uncertain test result means that a BRCA alteration was found but has not been associated with cancer in other people. One study found that about 10% of women undergoing BRCA testing had this type of ambiguous result. Altered genes other than BRCAs, as well as various inherited conditions, also are associated with an increased risk for breast and other cancers. These will not be detected with genetic screening for BRCA.

Deciding to be tested

A number of factors may influence the decision to be tested:

- Testing costs several hundred to several thousand dollars. Although some health plans cover genetic testing, many people do not want their insurance companies to know that they are even thinking about being tested for a genetic condition or predisposition.
- Many people want to know about any inherited risks for their children and other family members.
- Tests may give false negative or ambiguous results.
- Test results may influence important clinical decisions.

The results of genetic testing can have an impact on:

- emotions
- social relationships
- finances
- medical choices
- family relationships, since the tests can reveal information about other family members
- personal choices such as marriage and childbearing

A negative test result may:

- provide a sense of relief
- cause guilt over avoiding a disease that affects other family members
- eliminate the need for special preventative exams, tests, and surgeries
- provide a false sense of security, since the person still has the same cancer risk as the general population.

A positive test result may:

- provide relief from uncertainty
- cause anxiety, anger, or depression
- provide the opportunity to make informed decisions about the future
- force a choice concerning preventative measures that may have serious long-term implications with no guarantee of protection

Genetic discrimination

A positive test result for a BRCA mutation may put a person at risk for discrimination. Clinical test results usually are included in an individual's medical file, although some physicians choose not to include the results of genetic testing. However information about a person's genetic profile sometimes can be obtained from a family medical history. Medical records may be available to medical, life, and disability insurance companies, as well as employers.

A positive genetic test result may cause a person to be:

- denied medical coverage for expenses relating to their genetic condition
- dropped by their health plan
- unable to qualify for insurance

The Health Insurance Portability and Accountability Act (HIPPA) of 1996 prohibits employer-based group health plans from denying coverage on a genetic basis if the person does not have the disease. However employ-

ers can refuse to offer health coverage to that individual. Although several states prohibit genetic discrimination by employers and health insurance companies, decisions made in one state may have repercussions if the person moves to a different state.

Preventive measures

There are numerous risk factors for the development of breast and ovarian cancers. Most of these risk factors have not been evaluated in people carrying BRCA mutations.

Even thought mammograms do not detect some breast cancers, particularly in younger women such as those at-risk due to BRCA mutations, early diagnosis is very important for the prognosis of breast cancer. Women with a BRCA mutation should use augmented breast cancer surveillance techniques:

- monthly breast self-examinations beginning at age 18
- clinical breast examinations performed by a physician or nurse breast specialist every 6–12 months beginning at age 18
- mammograms every 6–12 months, beginning at age 25–35, or at least five years before the youngest age that breast cancer was diagnosed in a family member

Although it is unclear whether early detection of ovarian cancer increases survival rates, increased surveillance for ovarian cancer should begin at age 25–35, or 5–10 years before the youngest age that ovarian cancer was diagnosed in a family member. Surveillance includes:

- a pelvic examination every 6–12 months
- testing for CA-125—a blood protein marker for ovarian cancer— once or twice per year
- transvaginal or pelvic ultrasound once or twice per year

Chemoprevention includes treatment of a healthy at-risk woman with **tamoxifen** or other selective estrogen receptor modulators (SERMs). One study found that tamoxifen treatment reduced the incidence of breast cancer by 62% in women with an altered BRCA 2 gene but had no effect on women with an altered BRCA 1.

Risk-reducing, prophylactic, or preventive masectomy—the removal of the breasts and as much at-risk tissue as possible—in healthy women with a BRCA mutation reduces the risk of breast cancer by 90%. However it is not clear whether women undergoing this procedure are at any less risk of dying from breast cancer as compared with women who use careful surveillance methods.

KEY TERMS

185delAG—A deletion of DNA nucleotides deoxyadenylate (A) and deoxyguanylate (G) at nucleotide position 185 of the BRCA 1 gene; occurs in 1% of Ashkenazi Jews and causes susceptibility to breast and ovarian cancers.

5382insC—An insertion of the nucleotide deoxycytidylate (C) at nucleotide position 5382 of the BRCA 1 gene; occurs in 0.1% of Ashkenazi Jews and causes susceptibility to breast and ovarian cancers.

6174delT—A deletion of the nucleotide deoxythymidylate (T) at position 6174 of the BRCA 2 gene; occurs in 1.4% of Ashkenazi Jews and causes susceptibility to breast, ovarian, and prostate cancers.

Autosomal dominant—A non-sex-linked gene copy whose expression predominates over the other copy of the same gene, inherited from the other parent.

Mammogram—A breast x-ray used to detect cancer.

Mutation—An alteration or change in the DNA sequence of a gene.

Risk-reducing salpingo-oophorectomy, RRSO—Preventive or prophylactic surgical removal of the fallopian tubes and ovaries to reduce the risk of ovarian or breast cancers.

Selective estrogen receptor modulators (SERMs)—Drugs that selectively stimulate or inhibit the receptors for the hormone estrogen in different types of tissues.

Sporadic cancer—Cancers that occur without a genetic basis.

Tamoxifen—A SERM used to treat breast cancer and to help prevent breast cancer in women at high-risk for the disease.

Prophylactic or risk-reducing salpingo-oophorectomy (RRSO)—the removal of the fallopian tubes and ovaries—is estimated to reduce the risk of ovarian cancer by 95% in women with BRCA mutations. Surgical removal of the ovaries in pre-menopausal, high-risk women reduces their chance of developing breast cancer by about 50%. RRSO is recommended for high-risk women who have completed childbearing. Tubal ligation—the tying-off of the fallopian tubes—also may reduce the risk of developing ovarian cancer to a lesser extent. Unlike RRSO, tubal ligation does not result in the onset of menopause.

QUESTIONS TO ASK YOUR DOCTOR

- Am I at risk for breast and/or ovarian cancer because of my family history?
- Should I consider genetic testing?
- What are the advantages and disadvantages of genetic testing?
- What do positive, negative, or ambiguous test results mean?
- What are my choices if I test positive for a BRCA mutation?

However not all at-risk tissue can be removed by these procedures. Some women still develop breast, ovarian, or peritoneal cancers despite prophylactic surgery.

Resources

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ORGANIZATIONS

American Cancer Society. PO Box 102454, Atlanta, GA 30368-2454. 800-ACS-2345. <http://www.cancer.org>. Information, research, and patient support.

Cancer Genetics Network. Division of Cancer Control and Population Sciences, National Cancer Institute. 6130 Executive Boulevard, Executive Plaza North, Rockville, Maryland 20852. 301-594-6776. <http://epi.grants.cancer.gov/CGN>. A database and national network of centers for individuals and families and for research on genetic predispositions to cancer.

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Breast cancer

Definition

Breast cancer is caused by the development of malignant cells in the breast. The malignant cells often originate in the lining of the milk glands or ducts of the breast (ductal epithelium). Cancer cells are characterized by uncontrolled division leading to abnormal growth and the ability of these cells to invade normal tissue locally or to spread throughout the body, in a process called **metastasis**.

Description

Breast cancer often arises in the milk-producing glands of the breast tissue. Groups of glands in normal breast tissue are called lobules. The products of these glands are secreted into a ductal system that leads to the nipple. Depending on where in the glandular or ductal unit of the breast the cancer arises, it will develop certain characteristics that are used to sub-classify breast cancer into types. The pathologist will denote the subtype at the time of evaluation with the microscope. Ductal carcinoma begins in the ducts, and lobular carcinoma has a pattern involving the lobules or glands. The more important classification is related to the evaluated tumor's capability to invade, as this characteristic defines the disease as a true cancer. The stage before invasive cancer is called *in situ*, meaning that the early malignancy has not yet become capable of invasion. Thus, ductal carcinoma in situ is considered a minimal breast cancer.

How breast cancer spreads

The primary tumor begins in the breast itself but once it becomes invasive, it may progress beyond the breast to the regional lymph nodes or travel (metastasize) to other organ systems in the body and become systemic in nature. Lymph is the clear, protein-rich fluid that bathes the cells throughout the body. Lymph will work its way back to the bloodstream via small channels known as lymphatics. Along the way, the lymph is filtered through cellular stations known as nodes, thus they are called lymph nodes. Nearly all organs in the body have a primary lymph node group filtering the tissue fluid, or lymph, that comes from that organ. In the breast, the primary lymph nodes are under the armpit, or axilla. Classically, the primary tumor begins in the breast and the first place to which it is likely to spread is the regional lymph nodes. Cancer, as it invades in its place of origin, may also work its way into blood vessels. If cancer gets into the blood vessels, the blood vessels provide yet another route for the cancer to spread to other organs of the body.

Breast cancer follows this classic progression though it often becomes systemic or widespread early in the course of the disease. By the time one can feel a lump in the breast it is often 0.4 inches, or one centimeter, in size and contains roughly a million cells. It is estimated that a tumor of this size may take one to five years to develop. During that time, the cancer may metastasize.

When primary breast cancer spreads, it may first go to the regional lymph nodes under the armpit, the axillary nodes. If this occurs, regional metastasis exists. If it proceeds elsewhere either by lymphatic or blood-borne spread, the patient develops systemic metastasis that may involve a number of other organs in the body. Common sites of systemic involvement for breast cancer are the lung, bones, liver, and the skin and soft tissue. As it turns out, the presence of, and the actual number of, regional lymph nodes containing cancer remains the single best indicator of whether or not the cancer has become widely metastatic. Because tests to discover metastasis in other organs may not be sensitive enough to reveal minute deposits, the evaluation of the axilla for regional metastasis becomes very important in making treatment decisions for this disease.

If breast cancer spreads to other major organs of the body, its presence will compromise the function of those organs. Death can result from compromise of these vital organs' functions.

Demographics

Every woman is at risk for breast cancer. If she lives to be 85, there is a one out of nine chance that she will develop the condition sometime during her life. As a woman ages, her risk of developing breast cancer rises dramatically regardless of her family history. The breast cancer risk of a 25-year-old woman is only one out of 19,608; by age 45, it is one in 93. In fact, less than 5% of cases are discovered before age 35 and the majority of all breast cancers are found in women over age 50.

In 2002, 200,000 new cases of breast cancer were diagnosed. About 45,000 women die of breast cancer each year, accounting for 16% of deaths caused by cancer in women. However, deaths from breast cancer are declining in recent years, a reflection of earlier diagnosis from screening mammograms and improving therapies.

Causes and symptoms

There are a number of risk factors for the development of breast cancer, including:

- family history of breast cancer in mother or sister
- early onset of menstruation and late menopause
- reproductive history: women who had no children or have children after age 30 and women who have never breastfed have increased risk
- history of abnormal breast biopsies

Though these are recognized risk factors, it is important to note that more than 70% of women who get breast cancer have no known risk factors. Having several risk factors may boost a woman's chances of developing breast cancer, but the interplay of predisposing factors is complex. In addition to those accepted factors listed above, some studies suggest that high-fat diets, obesity, or the use of alcohol may contribute to the risk profile. Another factor that may contribute to a woman's risk profile is hormone replacement therapy (HRT).

HRT provides significant relief of menopausal symptoms, prevention of **osteoporosis**, and possibly protection from cardiovascular disease and **stroke**. While physicians have long known a small increased risk for breast cancer was linked to use of HRT, a landmark study released in 2003 proved the risk was greater than thought. The Women's Health Initiative found that even relatively short-term use of estrogen plus progestin is associated with increased risk of breast cancer, diagnosis at a more advanced stage of the disease, and a higher number of abnormal mammograms. The longer a woman used HRT, the more her risk increased.

Of all the risk factors listed above, family history is the most important. In *The Biological Basis of Cancer*, the authors estimate that probably about half of all familial breast cancer cases (families in which there is a high breast cancer frequency) have mutations affecting the genes BRCA-1 and BRCA-2. In 2003, scientists discov-

ered a third gene called EMSY. However, breast cancer due to heredity is only a small proportion of breast cancer cases; only 5%–10% of all breast cancer cases will be women who inherited a susceptibility through their genes. Nevertheless, when the family history is strong for development of breast cancer, a woman's risk is increased.

Not all lumps detected in the breast are cancerous. Fibrocystic changes in the breast are extremely common. Also known as **fibrocystic condition of the breast**, fibrocystic changes are a leading cause of non-cancerous lumps in the breast. Fibrocystic changes also cause symptoms of pain, swelling, or discharge and may become evident to the patient or physician as a lump that is either solid or filled with fluid. Complete diagnostic evaluation of any significant breast abnormality is mandatory because though women commonly develop fibrocystic changes, breast cancer is common also, and the signs and symptoms of fibrocystic changes overlap with those of breast cancer.

Diagnosis

The diagnosis of breast cancer is accomplished through **biopsy** of a suspicious lump or mammographic abnormality that has been identified. (A biopsy is the removal of tissue for examination by a pathologist. A mammogram is a low-dose, 2-view, x-ray examination of the breast.) The patient may be prompted to visit her doctor upon finding a lump in a breast, or she may have noticed skin dimpling, nipple retraction, or discharge from the nipple. The patient may not have noticed a symptom or abnormality, and a lump was detected by a screening mammogram.

When a patient has no signs or symptoms

Screening involves the evaluation of women who have no symptoms or signs of a breast problem. **Mammography** has been helpful in detecting breast cancer that cannot be identified on physical examination. However, 10%–13% of breast cancer does not show up on mammography, and a similar number of patients with breast cancer have an abnormal mammogram and a normal physical examination. These figures emphasize the need for examination as part of the screening process.

Screening

It is recommended that women get into the habit of doing monthly breast self examinations to detect any lump at an early stage. If an uncertainty or a lump is found, evaluation by an experienced physician and a mammogram is recommended. The American Cancer Society (ACS) has made recommendations for the use of mammography on a screening basis. In 2003, the ACS updated its guidelines concerning screening mammograms. The most notable change was that women should begin annual screening at age 40 instead of age 50. (in the past, the ACS, recommended beginning mammograms at age 40, but only ever one or two years instead of annually.) Women at higher risk for breast cancer should benefit from beginning screenings at earlier ages and at more frequent intervals.

Because of the greater awareness of breast cancer in recent years, screening evaluations by examinations and mammography are performed much more frequently than in the past. The result is that the number of breast cancers diagnosed increased, but the disease is being diagnosed at an earlier stage than previously. The earlier the stage of disease at the time it is discovered, the better the long-term outcome (prognosis) becomes.

When a patient has physical signs or symptoms

A common finding that leads to diagnosis is the presence of a lump within the breast. Skin dimpling, nipple retraction, or discharge from the nipple are less frequent initial findings prompting biopsy. Though bloody nipple discharge is distressing, it is most often caused by benign disease. Skin dimpling or nipple retraction in the presence of an underlying breast mass on examination is a more advanced finding. Actual skin involvement, with edema or ulceration of the skin, are late findings.

The presence of a breast lump is a common sign of breast cancer. If the lump is suspicious and the patient has not had a mammogram by this point, a study should be done on both breasts prior to anything else so that the original characteristics of the lesion can be studied. The opposite breast should also be evaluated mammographically to determine if other problems exist that were undetected by physical examination.

Whether an abnormal screening mammogram or one of the signs mentioned above followed by a mammogram prompted suspicion, the diagnosis is established by obtaining tissue by biopsy of the area. There are different types of biopsy, each utilized with its own indication depending on the presentation of the patient. If signs of widespread metastasis are already present, biopsy of the metastasis itself may establish diagnosis.

Biopsy

Depending on the situation, different types of biopsy may be performed. The types include incisional and excisional biopsies. In an incisional biopsy, the physician takes a sample of tissue, and in excisional biopsy, the mass is removed. Fine needle aspiration biopsy and core needle biopsy are kinds of incisional biopsies.

FINE NEEDLE ASPIRATION BIOPSY In a fine needle aspiration biopsy, a fine-gauge needle may be passed into the lesion and cells from the area suctioned into the needle can be quickly prepared for microscopic evaluation (**cytology**). (The patient experiencing nipple discharge can have a sample taken of the discharge for cytological evaluation, also.) Fine needle aspiration is a simple procedure that can be done under local anesthesia, and will tell if the lesion is a fluid-filled cyst or whether it is solid. The sample obtained will yield much diagnostic information. Fine needle aspiration biopsy is an excellent technique when the lump is palpable and the physician can easily hit the target with the needle. If the lesion is a simple cyst, the fluid will be evacuated and the mass will disappear. If it is solid, the diagnosis may be obtained. Care must be taken, however, because if the mass is solid and the specimen is non-malignant, a complete removal of the lesion may be appropriate to be sure.

CORE NEEDLE BIOPSY Core needle biopsies are also obtained simply under local anesthesia. The larger piece of tissue obtained with its preserved architecture may be helpful in confirming the diagnosis short of open surgical removal. An open surgical incisional biopsy is rarely needed for diagnosis because of the needle techniques. If there remains question as to diagnosis, a complete open surgical biopsy may be required.

EXCISIONAL BIOPSY When performed, the excisional, (complete removal) biopsy is a minimal outpatient procedure often done under local anesthesia.

NON-PALPABLE LESIONS As screening increases, non-palpable lesions demonstrated only by mammography are becoming more common. The use of x rays and computers to guide the needle for biopsy or to place markers for the surgeon performing the excisional biopsy are commonly employed. Some benign lesions can be fully removed by multiple directed core biopsies. These techniques are very appealing because they are minimally invasive; however, the physician needs to be careful to obtain a good sample.

Other tests

If a lesion is not palpable and has simple cystic characteristics on mammography, ultrasound may be utilized both to determine that it is a cyst and to guide its evacuation. Ultrasound may also be used in some cases to guide fine needle or core biopsies of the breast.

Computed tomography (CT) scans have only rare in the evaluation of breast lesions. **Magnetic resonance imaging** (MRI) has been used more often in recent years to follow up on suspicious findings from mammograms or for certain patients.

Clinical staging, treatments, and prognosis

Staging

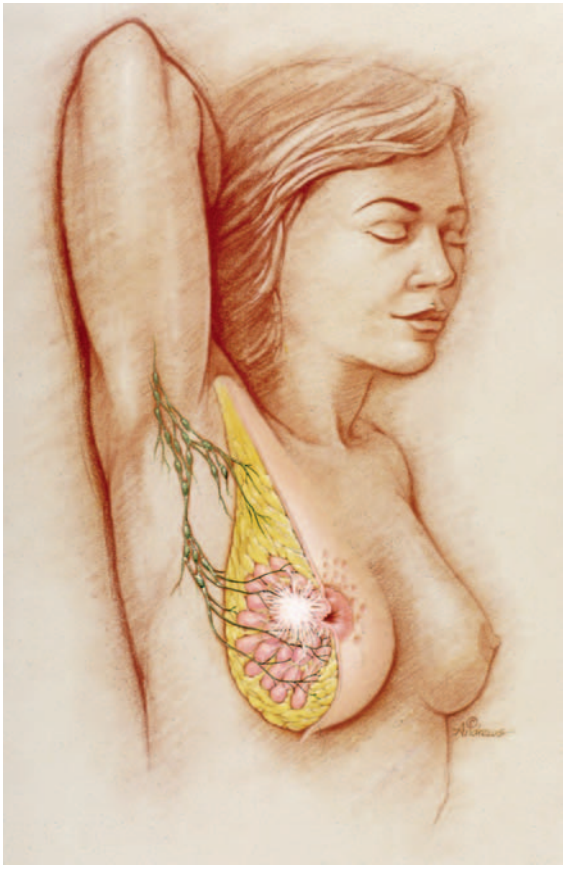
Once diagnosis is established, before treatment is rendered, more tests are done to determine if the cancer has spread beyond the breast. These tests include a chest **x ray** and blood count with liver function tests. Along with the liver function measured by the blood sample, the level of alkaline phosphatase, an enzyme from bone, is also determined. A radionuclear bone scan may be ordered. This test looks at the places in the body to which breast cancer usually metastasizes. A CT scan may also be ordered. The physician will do a careful examination of the axilla to assess likelihood of regional metastasis but unfortunately this exam is not very accurate. Since the axillary node status is the best reflection of possible widespread disease, some or all of these nodes may be removed at the time of surgical treatment. However, recent studies show great success with sentinel lymph node biopsy. This technique removes the sentinel lymph node, or that lymph node that receives fluid drainage first from the area where the cancer is located. If this node is free of cancer, staging can be assigned accordingly. This method saves women the discomfort and side effects associated with removing additional lymph nodes in her armpit.

Using the results of these studies, clinical stage is defined for the patient. This helps define treatment protocol and prognosis. After surgical treatment, the final, or pathologic, stage is defined as the true axillary lymph node status is known. Detailed staging criteria are available from the American Joint Commission on Cancer Manual and are generalized here:

- Stage 1—The cancer is no larger than 2 cm (0.8 in) and no cancer cells are found in the lymph nodes.
- Stage 2—The cancer is between 2 cm and 5 cm, and the cancer has spread to the lymph nodes.
- Stage 3A—Tumor is larger than 5 cm (2 in) or is smaller than 5 cm, but has spread to the lymph nodes, which have grown into each other.
- Stage 3B—Cancer has spread to tissues near the breast, (local invasion), or to lymph nodes inside the chest wall, along the breastbone.
- Stage 4—Cancer has spread to skin and lymph nodes beyond the axilla or to other organs of the body.

Treatment

Surgery, radiation, and **chemotherapy** are all utilized in the treatment of breast cancer. Depending on the stage, they will be used in different combinations or sequences to effect an appropriate strategy for the type and stage of the disease being treated.



The woman in this illustration has breast cancer. The tumor is visible in the breast, and the axillary lymph nodes reveal cancer as well. *(Custom Medical Stock Photo. Reproduced by permission.)*

SURGERY Historically, surgical removal of the entire breast and axillary contents along with the muscles down to the chest wall was performed as the lone therapy, (radical **mastectomy**). In the last 25 years, as it has been appreciated that breast cancer often spreads early, surgery remains a primary option but other therapies have risen in importance.

Today, surgical treatment is best thought of as a combination of removal of the primary tumor and staging of the axillary lymph nodes. A modified radical mastectomy involves removing the whole breast along with the entire axillary contents but not the muscles of the chest wall.

If the tumor is less than 4 cm (1.5 in) in size and located so that it can be removed without destroying the reasonable cosmetic appearance of the residual breast, just the primary tumor and a rim of normal tissue will be removed. The axillary nodes will still be removed for staging purposes, usually through a separate incision. Because of the risk of recurrence in the remaining breast tissue, radiation is used to lessen the chance of local recurrence. This type of primary therapy is known as **lumpectomy**, (or segmental mastectomy), and axillary dissection.

Sentinel **lymph node biopsy**, a technique for identifying which nodes in the axilla drain the tumor, has been developed to provide selective sampling and further lessen the degree of surgical trauma the patient experiences.

When patients are selected appropriately based on the preoperative clinical stage, all of these surgical approaches have been shown to produce similar results. In planning primary surgical therapy, it is imperative that the operation be tailored to fit the clinical circumstance of the patient.

The pathologic stage is determined after surgical treatment absolutely defines the local parameters. In addition to stage, there are other tests that are very necessary to aid in decisions regarding treatment. Handling of the surgical specimen is thus very important. The tissue needs to be analyzed for the presence or absence of hormone receptors and a receptor called HER-2. The presence of these receptors will influence additional therapies. Microscopic evaluation may also include the assessment of lymphatic or blood vessel invasion as these predict a worse outcome. The DNA of the tumor cells is quantitatively analyzed to help decide the biologic aggressiveness of the tumor. These parameters will be utilized collectively along with the axillary lymph node status to define the anticipated aggressiveness of the cancer. This assessment, along with the age and general condition of the patient, will be considered when planning the adjuvant therapies. Adjuvant therapies are treatments utilized after the primary treatment to help ensure that no microscopic disease exists and to help prolong patients' survival time.

RADIATION Like surgical therapy, **radiation therapy** is a local modality—it only treats the exposed tissue. Radiation is usually given post-operatively after surgical wounds have healed. The pathologic stage of the primary tumor is now known and this aids in treatment planning. The extent of the local surgery also influences the planning. Radiation may not be needed at all after modified radical mastectomy for stage I disease, but is almost always utilized when breast-preserving surgery is performed. If the tumor was extensive or if multiple nodes were involved, the field of tissue exposed will vary accordingly. Radiation is utilized as an adjunct to surgical therapy and is considered an important modality in gaining local control of the tumor. The use of radiation therapy does not affect decisions for adjuvant treatment.

In the past, radiation was used as an alternative to surgery on occasion. However, now that breast-preserving surgical protocols have been developed, primary radiation treatment of the tumor is no longer performed. Radiation also has an important role in the treatment of the patient with disseminated disease, particularly if it involves the skeleton. Radiation therapy can affect pain control and prevention of fracture in this circumstance.

DRUG THERAPY Many breast cancers, particularly those originating in post-menopausal women, are responsive to hormones. These cancers have receptors on their cells for estrogen and progesterone. Part of primary tumor assessment after removal of the tumor is the evaluation for the presence of these estrogen and progesterone receptors. If they are present on the cancer cells, altering the hormone status of the patient will inhibit tumor growth and have a positive impact on survival. The drug **tamoxifen** binds up these receptors on the cancer cells so that the hormones can't have an effect and, in so doing, inhibits tumor growth. If the patient has these receptors present, tamoxifen is commonly prescribed for five years as an adjunct to primary treatment. Adjuvant hormonal therapy with tamoxifen has few side effects but they have to be kept in mind, particularly the need for yearly evaluation of the uterus.

In late 2003, cancer experts were beginning to recommend a new group of drugs called aromatase inhibitors (Arimidex, common name anastrozole, or more recently Femara and Novartis, common name letrozole) as an alternative to tamoxifen. New guidelines also recommend letrozole following five years of tamoxifen therapy. These drugs fight breast cancer differently, but early research shows they fight it as effectively and with fewer side effects.

Shortly after the modified radical mastectomy replaced the radical mastectomy as primary surgical treatment, it was appreciated that survival after local treatment in stage II breast cancer was improved by the addition of chemotherapy. Adjuvant chemotherapy for an interval of four to six months is now standard treatment for patients with stage II disease. The addition of systemic therapy to local treatment in patients who have no evidence of disease is performed on the basis that some patients have metastases that are not currently demonstrable because they are microscopic. By treating the whole patient early, before widespread disease is diagnosed, the adjuvant treatment improves survival rates from roughly 60% for stage II to about 75% at five years after treatment. The standard regimen of CMF, or cytoxan, **methotrexate**, and **fluorouracil**, is given for six months and is well tolerated. The regimen of cytoxan, adriamycin (**doxorubicin**), and fluorouracil, (CAF), is a bit more toxic but only requires four months. (Adriamycin and cytoxin may also be used alone, without the fluorouracil.) The two methods are about equivalent in results. Adjuvant hormonal therapy may be added to the adjuvant chemotherapy as they work through different routes.

As one would expect, the encouraging results from adjuvant therapy in stage II disease have led to the study of similar therapy in stage I disease. The results are not as dramatic, but they are real. Currently, stage I disease is divided into categories a, b, and c on the basis of tumor size. Stage Ia is less than a centimeter in diameter. Adjuvant hormonal or chemotherapy is now commonly recommended for stage Ib and Ic patients. The toxicity of the treatment must be weighed individually for the patient as patients with stage I disease have a survivorship of over 80% without adjuvant chemotherapy.

If patients are diagnosed with stage IV disease or, in spite of treatment, progress to a state of widespread disease, systemic chemotherapy is utilized in a more aggressive fashion. In addition to the adriamycin-containing regimens, **docetaxel** and **paclitaxel**) have been found to be effective in inducing remission.

On the basis of certain prognostic factors, some patients with stage II or III disease can be predicted to do poorly. If their performance status allows, they may be considered for treatment with highly aggressive chemotherapy. The toxicity is such that bone marrow failure will result. To get around this anticipated side effect of the aggressive therapy, either the patients will be transplanted with their own stem cells, (the cells that will give rise to new marrow), or an allogeneic **bone marrow transplantation** will be required. This therapy can be a high-risk procedure for patients. It is given with known risk to patients predicted to do poorly and then only if it is felt they can tolerate it. Most patients who receive this therapy receive it as part of a clinical trial.

For patients who are diagnosed with advanced local disease, surgery may be preceded with chemotherapy and radiation therapy. The disease locally regresses allowing traditional surgical treatment to those who could not receive it otherwise. Chemotherapy and sometimes radiation therapy will continue after the surgery. The regimens of this type are referred to as neo-adjuvant therapy. This has been proven to be effective in stage III disease. Neo-adjuvant therapy is now being studied in patients with large tumors that are stage II in an effort to be able to offer breast preservation to these patients.

A drug known as Herceptin (**trastuzumab**), a monoclonal antibody, is now being used in the treatment of those with systemic disease. The product of the Human Epidermal Growth Factor 2 gene, (HER-2) is overexpressed in 25%–30% of breast cancers. Herceptin binds to the HER-2 receptors on the cancer, resulting in the arrest of growth of these cells.

Prognosis

The prognosis for breast cancer depends on the type and stage of cancer. Over 80% of stage I patients are cured by current therapies. Stage II patients survive overall about 70% of the time; those with more extensive lymph nodal involvement do worse than those with disease confined to the breast. About 40% of stage III patients survive five years, and about 20% of stage IV patients do so.

Coping with cancer treatment

Surgery for breast cancer is physically well-tolerated by the patient, especially those undergoing minimal surgery in the axilla. Most patients can return to a normal lifestyle within a month or so after surgery. Exercises can help the patient regain strength and flexibility. Arm, shoulder, and chest exercises help, and complete recovery of activity is to be expected.

About 5%–7% of patients undergoing complete axillary lymph node resection as part of their therapy may develop clinically significant lymphedema, or swelling in the arm on the side of involvement. If present, elevation and massage may be needed intermittently. Though usually not serious, on occasion this complication may interfere with complete physical recovery. The incidence of lymphedema is less with less axillary surgery. This is the reason for the enthusiasm for sentinel node biopsy as the surgical staging procedure in the axilla.

It is common after breast cancer treatment to be depressed or moody, to cry, lose appetite, or feel unworthy or less interested in sex. The breast is involved with a

KEY TERMS

Adjuvant therapy—Treatment involving radiation, chemotherapy (drug treatment), or hormone therapy, or a combination of all three given after the primary treatment for the possibility of residual microscopic disease.

Aneuploid—An abnormal number of chromosomes in a cell.

Aspiration biopsy—The removal of cells in fluid or tissue from a mass or cyst using a needle for microscopic examination and diagnosis.

Benign—Not malignant, noncancerous.

Biopsy—A procedure in which suspicious tissue is removed and examined by a pathologist for cancer or other disease. For breast biopsies, the tissue may be obtained by open surgery, or through a needle.

Estrogen-receptor assay—A test to see if a breast cancer needs estrogen to grow.

Hormones—Chemicals produced by glands in the body which circulate in the blood and control the actions of cells and organs. Estrogens are hormones which affect breast cancer growth.

Hormone therapy—Treating cancers by changing the hormone balance of the body, instead of by using cell-killing drugs.

Lumpectomy—A surgical procedure in which only the cancerous tumor in the breast is removed, together with a rim of normal tissue.

Lymph nodes—Small, bean-shaped masses of tissue scattered along the lymphatic system that act as filters and immune monitors, removing fluids, bacteria, or cancer cells that travel through the lymph system. Breast cancer cells in the lymph nodes under the arm or in the chest are a sign that the cancer has spread, and that it might recur.

Malignant—Cancerous.

Mammography—X-ray imaging of the breast that can often detect lesions in the tissue too small or too deep to be felt.

Oncogene—A gene that has to do with regulation of cell growth. An abnormality can produce cancer.

woman's identity and loss of it may be disturbing. For some, counseling or a support group can help. Many women have found a support group of breast cancer survivors to be an invaluable help during this stage. Involvement with volunteers from the local chapter of the Reach to Recovery program may be very helpful.

Nearly all patients undergo some form of adjuvant therapy for breast cancer. The magnitude of the toxicity of these adjuvant therapies is usually small and many patients receiving chemotherapy on this basis are capable of normal activity during this time. Certainly, those who progress to advanced disease are treated with more toxic chemotherapeutic regimens in an attempt to induce remission.

Clinical trials

The use of tamoxifen and other agents that alter the hormone status of the patient are under study. The National Surgical Adjuvant Breast and Bowel Project (NSABP) with support from the National Cancer Institute began a study in 1992 (called the Breast Cancer Prevention Trial, or BCPT). It researched the use of tamoxifen as a breast cancer preventive for high-risk women. The results yielded from the study showed that tamoxifen significantly reduced breast cancer risk, and the U.S. Food and Drug Administration approved the use of tamoxifen to reduce breast cancer risk for high-risk patients in 1998. Another NSABP study, known as STAR, has sought to understand if another drug, **raloxifene**, is as effective as tamoxifen in reducing breast cancer risk in high-risk patients. A number of clinical trials continue on the prevention and treatment of breast cancer. Numerous breast cancer organizations and the National Cancer Institute can provide information on participating in clinical trials.

Immune therapies have not been helpful to date though there are **vaccines** being developed against proteins such as that produced by HER-2 that may be beneficial in the future.

High-dose chemotherapy with bone marrow rescue remains controversial. Factors can be identified that predict certain patients will develop metastatic disease. This treatment has been offered to this select group of patients but the toxicity is such that defining a clear indication for this treatment remains under study.

Prevention

While most breast cancer can't be prevented, it can be diagnosed from a mammogram at an early stage when it is most treatable. The results of awareness and routine screening have allowed earlier diagnosis, which results in a better prognosis for those discovered.

Special concerns

Though breast-preserving therapy is being done more frequently than in years past, modified radical mastectomy remains an option when selecting therapy for the primary

QUESTIONS TO ASK THE DOCTOR

- Has my cancer spread?
- What is the stage of my cancer? What does that mean?
- What treatment choices do I have?
- What treatment do you recommend? Why?
- What are the advantages and disadvantages of this treatment?
- Will I lose my hair? If so, what can be done about it?
- What are the chances my cancer will come back after this treatment?
- What should I do to be ready for treatment?

tumor. This option may allow treatment without radiation in earlier stage patients, or may be necessary if the presentation of the tumor does not allow breast preservation. Loss of the breast is disfiguring and many patients so treated desire reconstruction of the breast. Breast reconstruction is performed either at the time of initial surgery (immediate) or it may be delayed. Alternatives include placement of implants or the rotation of muscle flaps from the abdomen or back. Most agree that breast preservation gives superior results to any form of reconstruction. When the breast is removed as part of primary therapy, these reconstructions are available and produce reasonable results. In 2003, research showed that young women who choose breast-conserving surgery are at higher risk for local recurrence and should receive indefinite follow-up care from their physicians.

See also Breast ultrasound; Sentinel lymph node mapping; Tumor staging.

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American Cancer Society. (800) ACS-2345. <http://www.cancer.org>.American Cancer Society's Reach to Recovery Program: <http://www2.cancer.org/bcn/reach.html>.

Cancer Care, Inc. (800) 813-HOPE. <http://www.cancercareinc.org>.

Cancer Information Service of the NCI. (1-800-4-CANCER). <http://wwwicic.nci.nih.gov>.

National Alliance of Breast Cancer Organizations. 9 East 37th St., 10th floor, New York, NY 10016. (888) 80-NABCO.

National Coalition for Cancer Survivorship. 1010 Wayne Ave., 5th Floor, Silver Spring, MD 20910. (301) 650-8868.

National Women's Health Resource Center. 2425 L St. NW, 3rd floor, Washington, DC 20037. (202) 293-6045.

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Breast Cancer Online. <http://www.bco.org/>.

National Alliance of Breast Cancer Organizations. <http://www.nabco.org/>.

National Cancer Institute. <http://rex.nci.nih.gov/PATIENTS/INFO_PEOPL_DOC.html>.

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Carol A. Turkington

Breast self-exam

Definition

Breast self-examination (BSE) is a diagnostic technique regularly performed by a woman, independent from a physician, both by feeling for anything suspicious in her breasts and by observing any changes through the use of a mirror.

Purpose

BSE should be performed monthly in order to discover changes in breast tissue, discharge from the nipple, or the onset of pain in the breast area. While 80% of lumps are not cancerous, such discoveries can ultimately lead to the detection of **breast cancer**.

Precautions

BSE is an effective self-diagnostic procedure, but it must not take the place of having a mammogram and having a health care provider check the breasts for abnormal changes. Make sure to schedule an annual clinical breast examination with a licensed medical care provider to supplement the BSE.

Description

It is important that BSEs are performed routinely so that a woman knows what her breasts normally feel and look like, resulting in quicker identification of anything abnormal. Self-exams take less than five minutes to perform and should be done a few days after the end of menstruation. Women that menstruate irregularly should choose a day of the month that is easy to remember, such as the date of their birth, and perform the exams on the same day each month.

The first phase of the BSE is to disrobe and stand in front of a mirror, observing the breast area in four different positions. First, with the arms down to the sides, look at the color, shape, outline, and direction of the breasts and nipples, taking note of anything atypical. Then, press the hands on the hips in order to flex the chest muscles, making the same observations. Next, observe the breasts while leaning forward. Finally, raise the arms overhead and notice anything abnormal such as color changes, dimpling of the skin, or nipple discharge.

The second phase of the BSE is performed lying down. First, put a pillow under the right shoulder and place the right hand under the head so that the elbow is positioned at a 90-degree angle. This is done in order to flatten the breast as much as possible, making the examination easier and more effective.

Woman examining her breast for abnormalities. *(Copyright Francoise Sauze, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Then, using the pads of the fingers of the left hand, press firmly around the breast using a small circular motion about the size of a penny. A small amount of lotion or petroleum jelly can make it easier to feel for lumps. Three types of pressure should be used. The first pressure should be enough to examine the surface, typically just to move the skin and feel for changes in the top layer of tissue. The second level of pressure is a deeper pressure, probing into the tissue. The final pressure level is applied deep into the breast tissue so that the rib cage can be felt and a minor amount of discomfort is experienced. Choose a comfortable pattern such as circles, lines, or wedges to make sure that the entire breast and armpit area are thoroughly examined with each level of pressure.

Finally, tenderly squeeze the area around the nipple and check for fluid discharge. After the right breast has been thoroughly examined, repeat the above steps on the left breast.

Although it is uncommon, forms of breast cancer can also occur in men. The breast self-exam can be modified to be effective for men. Men can utilize the visual exam and can also feel for any changes in the tissue.

Preparation

Since the patient performs BSE in the comfort of her own home, there are not many preparations that need to be made. The patient should remove any distractions that could interfere with the performance of a thorough exam. It is also advisable to disrobe and to use lotion or lubricant when palpating the breast area.

Aftercare

BSE is not an invasive procedure. Therefore there is not any significant aftercare that needs to take place.

KEY TERMS

Palpate—Examination by feeling and touching with the hands.

Individuals should simply remember to perform the exam monthly and inform their doctor of any changes.

Risks

There are no known risks associated with the breast self-exam as long as the individual schedules regular exams with a physician and immediately reports anything unusual.

Normal results

Patients who perform BSE regularly know what their breast tissue normally feels like. Typically, there will not be any detectable anomalies in their breast tissue, unless they carry out the exam just prior to menstruation or during pregnancy when breasts may seem more lumpy and tender. In these cases, it is likely that abnormal lumps and tenderness are not associated with cancerous tumors. However, if a woman finds anything that makes her uneasy, she should consult with her physician.

Abnormal results

Women should consult with their physician if they notice dimpling of the skin, any change in outline or shape of their breasts, unusual lumps, areas of thickening, or pain during the palpation of the breasts. If milky white or bloody discharge from the nipple is observed, then the patient should call the doctor. Generally, if there are any observations that make a person uneasy, it is advisable to contact a doctor.

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QUESTIONS TO ASK THE DOCTOR

- When should a mammogram be performed to complement the BSE?
- Do breast implants interfere with BSE?
- Do hormone supplements interfere with BSE?

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Sally C. McFarlane-Parrott

Breast ultrasound

Definition

Breast ultrasound (or sonography) is an imaging technique for diagnosing breast disease, such as cancer. It uses harmless, high-frequency sound waves to form an image (sonogram). The sound waves pass through the breast and bounce back or echo from various tissues to form a picture of the internal structures. It is not invasive and involves no radiation.

Purpose

Breast ultrasound may be used in several ways. The most common application is to investigate a specific area of the breast where a problem is suspected. A palpable lump and/or a lump or density discovered by **x ray** (mammogram) can be further evaluated by ultrasound. It is especially helpful in distinguishing between a fluid-filled cyst and a solid mass. It can also identify small lesions that are too tiny to be felt.

Breast ultrasound is often the first study performed to evaluate masses in women under 35 whose mammograms can be difficult to interpret due to the density of their breast tissue. In 2003, a new study found that ultrasound was more accurate than mammography at diagnosing breast cancer in women under age 45. However, mammography still works as a screening tool, with breast ultrasound as the follow-up examination. Another study in that year found that combining ultrasound with magnetic resonance imaging (MRI) direction greatly improved diagnostic decisions about breast cancer

lesions. The lesions detected by MRI could also be localized using ultrasound needle guidance for follow-up biopsy.

The lack of radiation used with ultrasound makes it ideal for studying breast abnormalities in women who are pregnant. Assessing breast implants for leakage or rupture is another way ultrasound is used. Breast inflammation, where pockets of infection or abscesses may form, can be diagnosed and monitored by ultrasound.

Thickened and swollen breast skin may be a sign of inflammatory **breast cancer**. Ultrasound can sometimes identify a cancerous growth within the breast causing the thickened skin. These cases are usually followed by a core **biopsy** guided by ultrasound (described below).

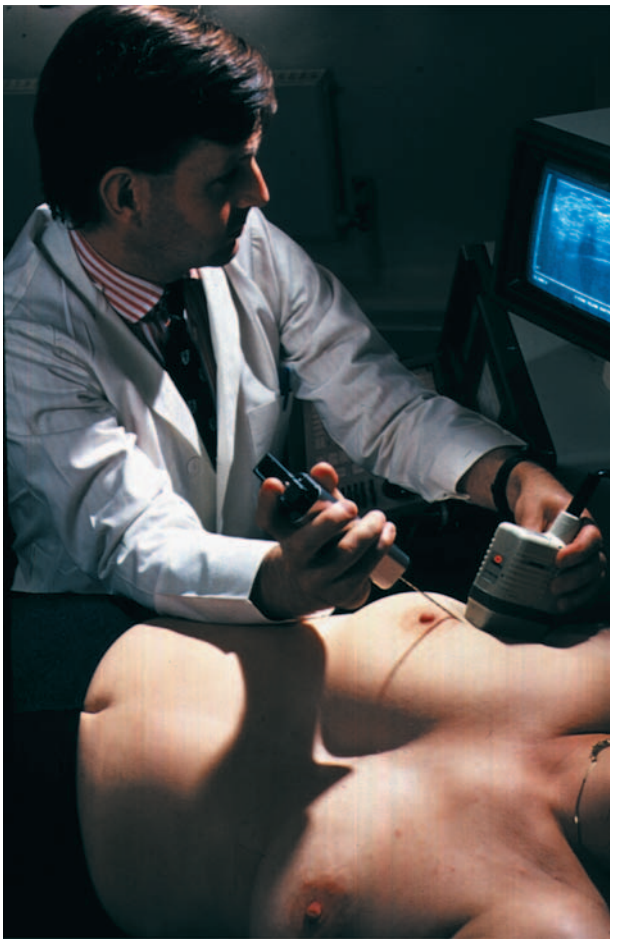
Breast ultrasound is employed to observe and guide a needle for several interventional procedures. These include cyst aspiration, fine needle aspiration, large core needle biopsy (as a first step in determining treatment for a lesion that is likely to be cancerous), and needle localization in surgical breast biopsy. Biopsies guided by ultrasound have distinct advantages. Patients usually find that the procedure is less traumatic and more comfortable than surgical biopsies. Ultrasound is known for its accuracy in determining how far a cancerous growth extends into the surrounding tissue in lesions that cannot be felt. Biopsies guided by ultrasound are generally less costly than surgical biopsies. Additionally, if the abnormality that requires biopsy can be seen on both a mammogram and ultrasound, an ultrasound-guided biopsy is often more comfortable for the patient as no compression is necessary.

Description

Ultrasound can be done in a doctor's office or another outpatient setting, such as a hospital or imaging center.

The patient removes her clothing from the waist up and puts on a hospital gown, open in the front. She lies on her back or side on an examining table. A gel that enhances sound transmission is spread over the area to be examined. The technologist then places a transducer, an instrument about the size of an electric shaver, against the skin. The images from reflected sound waves appear on a monitor screen.

A physician called a radiologist interprets the images obtained from ultrasound imaging. In 2003, it was reported that new computer-aided diagnosis (CAD) technology that had recently been widely added to mammography may help improve ultrasound as well. The CAD system uses computer algorithms applied to a three-dimensional ultrasound image to assign scores to mass characteristics. Though the technology will not replace human observation and judgment, it may soon be added to support the radiologist's interpretation.



This woman is having her breast scanned by ultrasound while a tissue biopsy is being taken. In breast scanning, ultrasound is used to distinguish between solid lumps and fluid-filled cysts. *(Photo by Geoff Tompkinson. Photo Researchers, Inc. Reproduced by permission.)*

A good ultrasound study is difficult to obtain if the patient is unable to remain quietly in one position. Obesity may hinder clear viewing of internal structures, and the accuracy of an ultrasound study is highly dependent on the skill of the person performing the examination. The images recorded vary with the angle and pressure of the transducer and the equipment settings. The examination may take from 30 to 45 minutes. Most insurance plans cover the cost of an ultrasound examination.

Normal results

An ultrasound examination may reveal either normal tissue or a benign condition such as a cyst. Ultrasound can confidently diagnose a benign structure that

KEY TERMS

Cyst—A thin-walled, fluid-filled benign structure in the breast.

Ductal carcinoma—A type of cancer that accounts for as much as 80% of breast cancers. These tumors feel bigger than they look on ultrasound or mammogram.

Fibroadenoma—A benign breast growth made up of fibrous tissue. It is the most common mass in women under 35 years of age, and is found in both breasts in 3% of cases.

Infiltrating lobular carcinoma—A type of cancer that accounts for 8% to 10% of breast cancers. In breasts that are especially dense, ultrasound can be useful in identifying these masses.

Microcalcifications—Tiny flecks that are too small to be felt. They are important markers of cancer that show up on ultrasound and mammogram.

Mucinous (colloid) carcinoma—A type of cancer that accounts for 1% to 2% of breast cancers. Resembles medullary carcinoma in ultrasound and mammogram, but usually affects older women.

Nonpalpable—Cannot be felt by hand. In cancer, growths that are nonpalpable are too small to be felt, but may be seen on ultrasound or mammogram.

Papillary carcinoma—A type of breast cancer that primarily occurs in older women. On ultrasound, this type of tumor may look like a solid or complex mass, or it may show up as solid tissue protruding into a cyst.

Tubular carcinoma—A type of cancer that accounts for approximately 1% to 2% of breast cancers. Can appear small on ultrasound or mammogram.

has certain characteristics of a simple cyst. In the case of a simple cyst with no symptoms, additional treatment beyond continued observation is usually not needed.

Abnormal results

A potentially malignant mass can be identified by breast ultrasound. Abnormal results fall into the following categories: benign fibrous nodule, complex cyst, suspicious lesion, and lesion highly suggestive of cancer. In cases where ultrasound shows the presence of a complex cyst or fibrous nodule, a biopsy is justified because 10% to 15% of these growths are malignant. Lesions falling into the last two categories (suspicious or highly suggestive of cancer) have a higher chance of being cancerous, and should be investigated further, either by biopsy or surgery.

Breast cancers such as the following may be identified on ultrasound: ductal **carcinoma**, infiltrating lobular carcinoma, medullary carcinoma, mucinous (colloid) carcinoma, tubular carcinoma, and papillary carcinoma. On ultrasound, the shape of a lesion and the type of edges it has can sometimes indicate if it is benign or cancerous, but there are exceptions. For example, benign fibroadenomas are usually oval, and some cancers can be similarly shaped. Cancerous tumors usually have jagged edges, but some benign growths can have these edges as well. Ultrasound is not a definitive test. Tissue diagnosis is often required.

See also Biopsy; Breast cancer; Breast self-exam.

QUESTIONS TO ASK THE DOCTOR

- Why is/was this procedure necessary?
- How long will the ultrasound take?
- What are the chances of finding an abnormal growth?
- Will the results be given during the procedure?
- If an abnormal growth is found, what is the next step?

Resources

PERIODICALS

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"CAD Software Improves Breast Ultrasound, Digital Mammograms." *Cancer Weekly* December 23, 2003: 13.

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Teresa G. Odle

Bronchoalveolar lung cancer

Definition

Bronchoalveolar lung cancer is a type of **non-small cell lung cancer**. The World Health Organization (WHO) classifies it as a subtype of **adenocarcinoma**.

Description

When a person breathes, air enters the trachea (windpipe). In the chest, the trachea splits into two passageways called bronchi. One goes to the right lung and the other to the left lung. The bronchi then subdivide into smaller tubes called bronchioles. These bronchioles end in tiny air sacs called alveoli. A diagram of the respiratory system resembles an upside down tree with the trachea as the tree trunk and the alveoli as the leaves. Exchange of gasses between the lungs and the blood occurs in the alveoli.

Lung cancer, like all cancers, is the result of uncontrolled cell growth. The specific characteristics of each cancer depend on which cells are growing out of control and where they are located. There are two distinct types of lung cancer each with its own characteristics and treatment strategies—small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

NSCLC can develop from several different types of lung cells, so it is further categorized as either squamous cell **carcinoma**, adenocarcinoma, or large-cell lung cancer. Bronchoalveolar lung cancer is a subtype of adenocarcinoma.

Bronchoaveolar lung cancer is a primary malignant cancer of the lungs, meaning that the lungs are the first place this cancer develops; it does not migrate to the lungs from elsewhere in the body. Bronchoalveolar cancer usually develops in the outer (peripheral) regions of the lungs in gland-like cells that secrete mucus. It spreads along the membranes that separates the alevoli from each other.

Research published in 2003 suggests that there are two patterns to the development of bronchoalveolar cancer. In about 40–80% of cases, these cancer cells are found in a limited area of the lung, making surgery a possible treatment. In the remainder of the cases, they are spread out over a wide area. Regardless of how these cells are distributed, they look identical, and they are often mixed in with other adenocarcinoma cells.

Demographics

Lung cancer is leading cause of cancer deaths in the United States. The American Cancer Society predicted about 172,500 new cases of lung cancer (all types) would develop in 2005, accounting for about 13% of all new cancers. Lung cancer occurs primarily in people over age 45, and is slightly more likely to occur in men than in women.

Adenocarcinoma accounts for about 40% of all lung cancers, up from about 13% in 1965. The number of lung cancer cases attributed to adenocarcinoma is increasing rapidly in the United States and Europe, especially in women, although cases are also increasing among men. Bronchoalveolar cancer is thought to account for between 2% and 14% of all cases of lung cancer. About 85% of lung cancers can be attributed to smoking tobacco. However, although smoking **cigarettes** increases the risk of developing bronchoalveolar cancer, it is the most common type of lung cancer found among individuals who have never smoked cigarettes.

Causes and symptoms

In general, lung cancers develop because of acquired changes that occur in the genes of lung cells when they are exposed to carcinogens such as tobacco smoke. These changes either turn on genes that cause cells to grow uncontrollably (oncogenes) or turn off genes that cause cells to die at the appropriate time (tumor suppressor genes) or both.

Because bronchoalveolar cancer is the most likely lung cancer to develop among people who have never smoked, its exact cause is somewhat unclear. Like all lung cancers, smoking tobacco or marijuana, exposure to asbestos, and inhalation certain workplace chemicals (e.g. radon gas, arsenic, beryllium, vinyl chloride, coal products, gasoline exhaust) increases the risk of developing bronchoalveolar cancer. However, since this type of cancer is increasing and is common among non-smokers, some other yet to be determined factors seem to play a role in its development.

Lung cancer symptoms tend to develop only after the cancer is far advanced and possibly has even spread (metastasized) to other placed in the body such as the liver, adrenal glands, bones, or brain. Bronchoalveolar cancer is no exception. When symptoms do occur, they include:

- coughing
- difficulty breathing
- chest pain
- weight loss

Bronchoalveolar lung cancer causes the cells lining the lungs to produce a lot of mucus. When examined by a doctor, the lungs may have an abnormal dead or dull sound because of the amount of mucus they contain. Severity of symptoms, however, is not well correlated to the severity or stage of this cancer.

Diagnosis

Diagnostic tests are the same as for any suspected lung cancer, beginning with a chest x ray and moving on to other **imaging studies** such as **computed tomography** (CT) scan, **magnetic resonance imaging** (MRI), ultrasound, and **positron emission tomography** (PET) scans. Initial tests determine the presence and extent of suspected cancer in the lungs, while later tests are done to determine if the cancer has metastasized to other sites. A sample of sputum (coughed up mucus) may be examined for cancer cells, but the definitive diagnosis is made by taking a **biopsy** of lung tissue.

Treatment team

The treatment team will most likely include a medical oncologist, radiation oncologist, thoracic surgeon, pulmonologist, oncology nurse, and social worker.

Clinical staging, treatments, and prognosis

The staging, treatment, and prognosis for bronchoalveolar lung cancer is the same as for other NSCLS. The stage of the cancer is based on the TNM system. This considers the tumor size and how much it has grown (T), whether the cancer has spread to the lymph nodes (N) and whether it has metastasized (M) to distant sites in the body.

Stage IA

T1 N0 M0. The tumor is no larger than 3 cm (about 1.2 in) with no sign of lymph node involvement or **metastasis**. Treatment at this stage is likely to involve only surgery to remove the tumor. Surgery can remove one lobe of the lung (**lobectomy**) or a part of a lobe (wedge resection or **segmentectomy**). The estimated five-year survival rate when NSCLC is treated at this stage is 75%, however lung cancer is rarely diagnosed this early.

Stage IB

T2 NO MO. The tumor is larger than 3 cm, but cancer has not spread beyond the lung. Treatment is usually surgery. Sometimes **radiation therapy** is recommended following surgery. The estimated five-year survival rate when NSCLC is treated at this stage is 55%.

Stage II A

T1 N1 MO. The tumor is smaller than 3 cm, but cancer has spread locally to the lymph nodes, although it has not metastasized to distant sites. Treatment at this stage is usually surgery to remove a lobe of the lung or sometimes the entire lung. (Individuals can survive well with a single lung.) Radiation therapy may follow surgery. Supplemental **chemotherapy** at this stage is being studied in **clinical trials**. The estimated five-year survival rate when NSCLC is treated at this stage is 50%.

Stage II B

T2 N1 MO or T3 N0 M0. Either the individual's condition is the same as in stage IIA except that the tumor is larger than 3 cm, or the tumor has grown into the membrane surrounding the lungs, the chest cavity, diaphragm, or membrane surrounding the heart. Treatment is similar to stage IIA. The estimated five-year survival rate when NSCLC is treated at this stage is 40%.

Stage III A

T1-3 N2 MO or T3 N1 M0. The tumor can be any size, but cancer has spread to additional, more distant lymph nodes, but has not metastasized to distant sites. Alternately, the tumor is growing into the surrounding membranes or muscles, but only local lymph nodes are involved. Treatment at this stage depends on where in the lung the cancer is located. Most bronchoalveolar cancers are located on the edges of the lung. Surgery of the lung and lymph nodes may be performed depending on where the tumor is located, but chemotherapy and radiation therapy are also required. The estimated five-year survival rate when NSCLC is treated at this stage is 10–35% depending in part on whether the tumor is operable.

Stage III B

Any T4 or N3 and M0. The tumor has invaded nearby organs such as the esophagus, trachea, large blood vessels or heart or the cancer has spread to large and diverse lymph nodes, although it has not metastasized to distant organs. Surgery at this stage will not removed the cancer. Individuals in good health undergo chemotherapy and radiation therapy. The estimated five-year survival rate when NSCLC is treated at this stage is less than 5%.

Stage IV

Any M1. Cancer has metastasized to distant organs. Stage IV cancer is almost incurable. The goal of treatment is to improve the quality of life or extend life. Aggressive chemotherapy may be used for individuals in otherwise good health. Alternately, care may be given to make the individual as comfortable as possible. The estimated five-year survival rate when NSCLC is treated at this stage is about 2%.

Alternative and complementary therapies

Although many alternative therapies are said to protect against developing cancer, few claim to cure lung cancer. At one time, large doses of vitamin A and beta-carotene found in yellow and dark green vegetables were promoted as decreasing the risk of lung cancer. However, according to the National Institutes of Health Office of Dietary Supplements, in a controlled, randomized study, researchers found that smokers taking vitamin A and beta -carotene supplements were 46% more likely to die of lung cancer than smokers who did not take these supplements.

Acupuncture has proved effective in many people to deal with the nausea associated with chemotherapy.

Unlike traditional pharmaceuticals, complementary and alternative therapies are not evaluated by the United States Food and Drug Administration (FDA) for either safety or effectiveness. Patients should be wary of "miracle cures" and tell their doctors if they are using herbal remedies, vitamin supplements or other unprescribed treatments. Alternative and experimental treatments normally are not covered by insurance.

Coping with cancer treatment

Lung cancer is often not diagnosed until it is too far advanced to be cured, The overall long-term survival rate for individuals with lung cancer is about 13%. In addition to coping with the psychological stress of cancer, individuals face many unpleasant side effects from treatment, such as nausea, vomiting, **fever**, and weakness. New drugs have improved the control of nausea and pain, but not eliminated the problem.

Hospitals and cancer centers provide social workers to help families cope with changes brought on by cancer ranging from finding a transportation to and from treatments to the financial stress of illness to preparing for impending death. Religious counseling and support is also available, as are support groups for those afflicted with specific cancers and their family members. **Hospice care** can help the individual maintain some control over their quality of life in the event of terminal cancer.

KEY TERMS

Medical oncologist—A physician who specializes in treating cancer patients.

Pulmonologist—A physician who specializes in the lung and respiratory disorders.

Radiation oncologist—A physician that specializes in radiation therapy for cancer patients.

Sputum—Mucus that is coughed up from the lungs.

Clinical trials

Because NSCLC is one of the more common cancers, many clinical trials are underway to determine the effectiveness of new drugs and new therapies. A list of clinical trials that are currently recruiting patients with bronchoalveolar lung cancer can be found by entering the search term "bronchoalveolar lung cancer" at the following web sites:

- National Cancer Institute <http://cancer-trials.nci.nih.gov> or 1-800-4-CANCER
- National Institutes of Health Clinical Trials <http://clinicaltrials.gov>
- Center Watch: A Clinical Trials Listing <http://www.centerwatch.com>.

Some of these trials involve experimental medications, while others involve various combinations of chemotherapy and radiation therapy.

Prevention

Avoiding smoking is the best way to prevent all lung cancers. Between 85% and 90% of people who develop lung cancer are smokers. No matter how long or how much an individuals has smoked, the chance of getting lung cancer decreases and general health improves by quitting smoking.

Other ways to prevent all lung cancers include avoiding breathing gasoline and diesel fuel fumes and exposure to asbestos and other airborne chemicals known to be carcinogens. Maintaining a healthy weight, exercising regularly, and eating a diet high in vegetables and fruits are other positive steps individuals can take. Some nutritionist advise including 5–10 cups of green

QUESTIONS TO ASK YOUR DOCTOR

- What type of lung cancer do I have?
- What stage is my cancer?
- Why do you recommend this particular treatment and what are the alternatives?
- What kind of side effects can I expect from treatment?
- Are there any clinical trials that might be appropriate for me?

tea daily in the diet because of green tea's antioxidant properties. However, all these diet and exercise precautions are of minor importance when compared to the preventative effects of not smoking.

Special concerns

Individuals with lung cancer often show no symptoms until their cancer is far advanced. Studies have found that regular chest **x rays** or CT scans of smokers' lungs do not increase the rate of early detection.

Resources

PERIODICALS

Dumont, Pascal, et al. "Bronchoalveolar carcinoma: Histopathologic Study of Evolution in a Series of 105 Surgically Treated Patients" *Chest* 113, no.2 (February 1998):391-396.

Rachita, Mircea et al. "Bronchoalveolar Carcinoma in a 58-Year-Old Man," *Consultant*. 43, no. 3 (March 2003): 357-360.

ORGANIZATIONS

American CancerSociety. 1599 Clifton Road NE, Atlanta GA 30329-4251. 1-800-ACS-2345. <http://www.cancer.org>.

National Cancer Institute Information Line 1-800-4-CANCER (1-800-422-6237) <http://www.cancer.gov>. cancergovstaff@mail.nih.gov.

OTHER

American Cancer Society. *Lung Cancer,* 12 November 2004 [cited 6 March 2005]. <http://www.cancer.org/docroot/CRI/CRI_2_3x.asp?dt=26>.

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Tish Davidson, A.M.

Bronchoscopy

Definition

Bronchoscopy is a procedure in which a cylindrical fiberoptic scope is inserted into the airways. This scope contains a viewing device that allows the visual examination of the lower airways.

Purpose

During a bronchoscopy, a physician can visually examine the lower airways, including the larynx, trachea, bronchi, and bronchioles. The procedure is used to examine the mucosal surface of the airways for abnormalities that might be associated with a variety of lung diseases. Its use includes the visualization of airway obstructions such as a tumor, or the collection of specimens for the diagnosis of cancer originating in the bronchi of the lungs (bronchogenic cancer). It can also be used to collect specimens for culture to diagnose infectious diseases such as tuberculosis. The type of specimens collected can include sputum (composed of saliva and discharges from the respiratory passages), tissue samples from the bronchi or bronchioles, or cells collected from washing the lining of the bronchi or bronchioles. The instrument used in bronchoscopy, a bronchoscope, is a slender cylindrical instrument containing a light and an eyepiece. There are two types of bronchoscopes, a rigid tube that is sometimes referred to as an open-tube or ventilating bronchoscope, and a more flexible fiberoptic tube. This tube contains four smaller passages—two for light to pass through, one for seeing through and one that can accommodate medical instruments that may be used for **biopsy** or suctioning, or that medication can be passed through.

Bronchoscopy may be used for the following purposes:

- to diagnose cancer, tuberculosis, lung infection, or other lung disease
- to examine an inherited deformity of the lungs
- to remove a foreign body in the lungs, such as a mucus plug, tumor, or excessive secretions
- to remove tissue samples, also known as biopsy, to test for cancer cells, help with staging the advancement of the lung cancer, or to treat a tumor with laser therapy
- to allow examination of a suspected tumor, obstruction, secretion, bleeding, or foreign body in the airways
- to determine the cause of a persistent cough, wheezing, or a cough that includes blood in the sputum
- to evaluate the effectiveness of lung cancer treatments

Precautions

Patients not breathing adequately on their own due to severe respiratory failure may require mechanical ventilation prior to bronchoscopy. It may not be appropriate to perform bronchoscopy on patients with an unstable heart condition. All patients must be constantly monitored while undergoing a bronchoscopy so that any abnormal reactions can be dealt with immediately.

Description

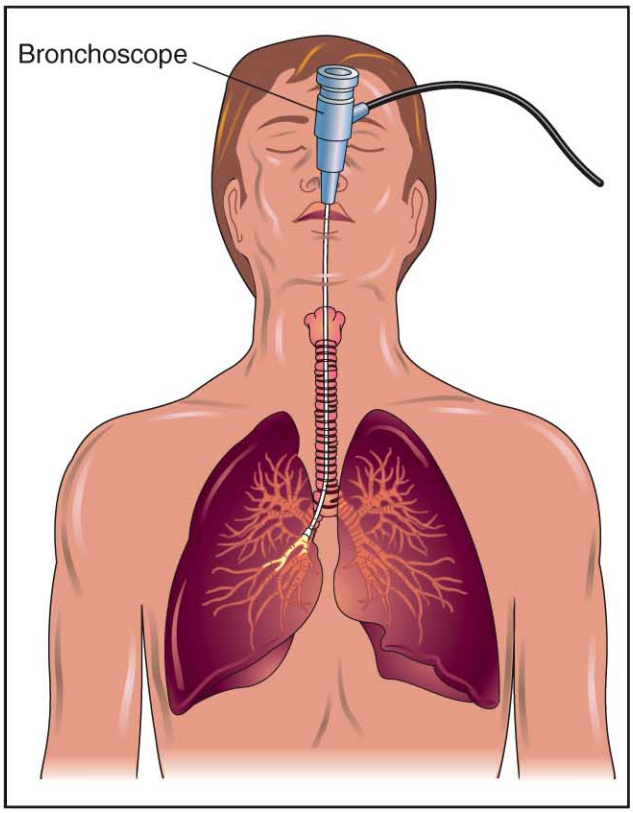
There are two types of bronchoscopes, a rigid tube and a fiberoptic tube. Because of its flexibility, the fiberoptic tube is usually preferred. However, if the purpose of the procedure is to remove a foreign body caught in the windpipe or lungs of a child, the more rigid tube must be used because of its larger size. The patient will either lie face-up on his/her back or sit upright in a chair. Medication to decrease secretions, lessen anxiety, and relax the patient are often given prior to the procedure. While breathing through the nose, anesthesia is sprayed into the mouth or nose to numb it. It will take 1-2 minutes for the anesthesia to take effect. Once this happens, the bronchoscope will be put into the patient's mouth or nose and moved down into the throat. While the bronchoscope is moving down the throat, additional anesthesia is put into the bronchoscope to numb the lower parts of the airways. Using the eyepiece, the physician then observes the trachea and bronchi, and the mucosal lining of these passageways, looking for any abnormalities that may be present.

If the purpose of the bronchoscopy is to take tissue samples or biopsy, forceps or a bronchial brush are used to obtain cells. If the purpose is to identify an infectious agent, a bronchoalveolar lavage (BAL) can be used to gather fluid for culture purposes. Also, if any foreign matter is found in the airways, it can be removed.

Another procedure using bronchoscopy is called fluorescence bronchoscopy. This can be used to detect precancerous cells present in the airways. By using a fluorescent light in the bronchoscope, precancerous tissue will appear dark red, while healthy tissue will appear green. This technique can help detect lung cancer at an early stage, so that treatment can be started early.

Alternative procedures

Depending upon the purpose of the bronchoscopy, alternatives might include a **computed tomography** scan (CT) or no procedure at all. Bronchoscopy is often performed to investigate an abnormality that shows up on a chest **x ray** or CT scan. If the purpose is to obtain biopsy specimens, one option is to perform surgery, which carries greater risks. Another option is percutaneous (through the skin) biopsy guided by computed tomography.



Bronchoscopy is a procedure in which a hollow, flexible tube is inserted into the airways, allowing the physician to visually examine the lower airways, including the larynx, trachea, bronchi, and bronchioles. It can also be used to collect specimens for bacteriological culture to diagnose infectious diseases such as tuberculosis. *(Illustration by Electronic Illustrators Group.)*

Preparation

The doctor should be informed of any allergies and all the medications that the patient is currently taking. The doctor may instruct the patient not to take medications like aspirin or anti-inflammatory drugs, which interfere with clotting, for a period of time prior to the procedure. The patient needs to fast for 6 to 12 hours prior to the procedure and refrain from drinking any liquids the day of the procedure. The bronchoscopy takes about 45 to 60 minutes, with results usually available in one day. Prior to the bronchoscopy, several tests may be done, including a chest x ray and blood work. Sometimes a bronchoscopy is done under general anesthesia. Patients usually have an intravenous (IV) line in the arm. Most likely, the procedure will be done under local anesthesia, which is sprayed into the nose or mouth. This is necessary to decrease the gag reflex. A sedative may also

KEY TERMS

Anesthesia—A drug used to induce loss of sensation. It is used to lessen the pain of surgery and medical procedures.

Bronchi—The network of tubular passages that carry air to the lungs and allow air to be expelled from the lungs.

Bronchioles—Small airways extending from the bronchi into the lobes of the lungs.

Bronchoalveolar lavage—Washing cells from the air sacs at the end of the bronchioles.

Trachea—The windpipe.

be used to help the patient relax. It is important that the patient understands that at no time will the airway be blocked and that oxygen can be supplied through the bronchoscope. A signed consent form is necessary for this procedure.

Aftercare

After the bronchoscopy, the patient will be monitored for vital signs such as heart rate, blood pressure, and breathing, while resting in bed. Sometimes patients have an abnormal reaction to anesthesia. All saliva should be spit into a basin so that it can be examined for the presence of blood. If a biopsy was taken, the patient should not cough or clear the throat as this might dislodge any blood clot that has formed and cause bleeding. No food or drink should be consumed for about two hours after the procedure or until the anesthesia wears off. Diet is gradually progressed from ice chips and clear liquids to the patient's regular diet. There will also be a temporary sore throat and hoarseness that may last for a few days.

Risks

Minor side effects arise from the bronchoscope causing abrasion of the lining of the airways. This results in some swelling and inflammation, as well as hoarseness caused from abrading the vocal cords. If this abrasion is more serious, it can lead to respiratory difficulty or bleeding of the airway lining. A more serious risk involved in having a bronchoscopy performed is the occurrence of a pneumothorax, due to puncturing of the lungs, which allows air to escape into the space between the lung and the chest wall. These risks are greater with the use of a rigid bronchoscope than with a fiberoptic bronchoscope. If a rigid tube is used, there is also a risk of chipped teeth.

QUESTIONS TO ASK THE DOCTOR

- Did you see any abnormalities?
- How soon will you know the results of the biopsy (if one was done)?
- When can I resume any medications that were stopped?
- What future care will I need?
- For what type of problems should I call you?

Normal results

Normal tracheal appearance consists of smooth muscle with C-shaped rings of cartilage at regular intervals. The trachea and the bronchi are lined with a mucous membrane.

Abnormal results

Abnormal bronchoscopy findings may involve abnormalities of the bronchial wall such as inflammation, swelling, ulceration, or anatomical abnormalities. The bronchoscopy may also reveal the presence of abnormal substances in the trachea and bronchi. If samples are taken, the results could indicate cancer, disease-causing agents or other lung disease. Other abnormalities include constriction or narrowing (stenosis), compression, dilation of vessels, or abnormal branching of the bronchi. Abnormal substances that might be found in the airways include blood, secretions, or mucous plugs. Any abnormalities are discussed with the patient.

Resources

BOOKS

Fauci, Anthony S. *Harrison's Principles of Internal Medicine*. 14th ed. New York: McGraw-Hill, 2000.

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Burkitt's lymphoma

Definition

Burkitt's lymphoma (BL) is a type of non-Hodgkin's lymphoma (NHL) that is sometimes called a B-cell lymphoma or small noncleaved cell lymphoma. It

is an endemic (characteristic of a specific place) disease in central Africa but sporadic (occurring in scattered instances) in other countries. Burkitt's lymphoma is one of the most rapidly growing forms of human cancer. In addition, the number of new cases of this tumor is rising in most countries.

Description

Burkitt's lymphoma was first described in 1957 by Denis Parsons Burkitt, an Irish surgeon. While this type of lymphoma is still relatively rare in the United States, it is responsible for 50% of cancer deaths in children in Uganda and central Africa. The endemic form of Burkitt's lymphoma is characterized by rapid enlargement of the patient's jaw, loosening of the teeth, protruding eyeballs, or an abdominal tumor in the region of the kidneys or ovaries.

In the sporadic form of Burkitt's, the patient may have a facial tumor but is much more likely to have an abdominal swelling, often in the area of the ileocecal valve (the valve between the lower portion of the small intestine and the beginning of the large intestine). About 90% of American children with Burkitt's have abdominal tumors. Others may develop tumors in the testes, ovaries, skin, nasal sinuses, or lymph nodes. In adults, Burkitt's lymphoma frequently produces a bulky abdomen and may involve the liver, spleen, and bone marrow.

Demographics

In Western countries, Burkitt's lymphoma is more common in male than in female children. While the average age of patients with endemic Burkitt's is seven years, outside Africa the average age is closer to 11 years. In the United States, the **non-Hodgkin's lymphomas** as a group account for about 7% of cancers in persons under 20 years of age. Between 40% and 50% of these cases are Burkitt's lymphoma.

In adults, Burkitt's lymphoma is again more common in males than in females. It is 1,000 times more common in persons with AIDS than in the general population. Currently, about 2% of AIDS patients develop Burkitt's lymphoma. The majority of these patients have stage IV disease by the time the tumor is diagnosed.

Causes and symptoms

Causes

ONCOGENES Burkitt's lymphoma affects a part of the immune system known as the lymphatic or lymphoid system. The lymphatic system is a network of tissues, glands, and channels that produces lymphocytes, a type of white blood cell. Some lymphocytes remain in clusters within the lymph nodes, while others circulate throughout the body in the bloodstream or in the lymph, which is a clear yellowish fluid carried by the lymphatic channels. Lymphocytes fall into two groups: T cells, which regulate the immune system; and B cells, which produce antibodies. Burkitt's lymphoma involves the B-cell lymphocytes. In 1982, researchers discovered an oncogene (a gene that can release cells from growth constraints, possibly converting them into tumors) in 90% of patients with Burkitt's lymphoma. Called the C-*myc* oncogene, it is responsible for the uncontrolled production of B-lymphocytes. It results from a translocation, or exchange, of genetic material between the long arm of human chromosome 8 and the long arm of human chromosome 14. In a smaller number of patients with Burkitt's, the translocation involves chromosomes 2 and 22 or chromosomes 2 and 8.

In the summer of 2000, researchers reported that a gene called the HMG-I/Y gene is also involved in the development of Burkitt's lymphoma. The C-*myc* oncogene appears to stimulate the HMG-I/Y gene, which then triggers the changes in normal B cells that cause them to multiply rapidly and form tumors.

VIRUSES In addition to translocations of genetic material, Burkitt's lymphoma is also associated with oncogenic viruses—the **Epstein-Barr virus** (EBV) in endemic Burkitt's and human immunodeficiency virus (HIV) in the sporadic form. EBV, or human herpesvirus 4, is the virus that causes infectious mononucleosis. The presence of EBV in patients with endemic Burkitt's has been interpreted as a side effect of the high rates of malaria in central Africa. African children may have immune systems that cannot fight off infection with EBV because they have been weakened by malaria. The children's B-lymphocytes then reproduce at an unusually high rate. Currently, however, the precise role of EBV in Burkitt's lymphoma is still being investigated, because the virus is less common in patients outside Africa. In the United States, about 25% of children and 40% of adult AIDS patients with Burkitt's have the Epstein-Barr virus.

Symptoms

In children, symptoms may appear as soon as four to six weeks after the lymphoma begins to grow. The more common symptom pattern is a large tumor in the child's abdomen accompanied by fluid buildup, pain, and vomiting. If the lymphoma begins in the blood marrow, the child may bleed easily and become anemic.

In adults, the first symptoms of Burkitt's lymphoma may include swelling in a lymph node in the upper body or a swollen and painful abdomen. If the tumor is located

African child with facial disfigurement caused by Burkitt's lymphoma. *(Custom Medical Stock Photo. Reproduced by permission.)*

in the chest, it may put pressure on the airway and cause difficulty in breathing. There may be unexplained **itching** or **weight loss**. Other patients may have more general symptoms, such as **fever** or a loss of energy. Adults with AIDS often have tumors developing in several different locations in the body by the time they are diagnosed.

Diagnosis

Burkitt's lymphoma is usually diagnosed by examining a piece of tissue from a surgical **biopsy** of a swollen area in the patient's body—often the jaw area in endemic Burkitt's or the abdomen in the sporadic form. The tissue is examined under a microscope by a pathologist, who is a physician with special training in the study of tissue or body fluid samples. In Burkitt's lymphoma, the tumor cells will show a very high rate of cell division and a characteristic "starry sky" pattern. The pathologist may also test the tissue sample for the presence of EBV, which is found in about 30% of patients diagnosed with Burkitt's lymphoma in the United States.

In addition to a tissue biopsy, the patient is also given a complete blood count (CBC) test, a platelet count, and a **lumbar puncture** (spinal tap). A small sample of bone marrow is usually taken as well. Most cases of Burkitt's lymphoma do not require extensive x rays, although CT (**computed tomography**) scans of the chest and abdomen are usually taken, as well as a **gallium scan**. This scan involves being injected with the radioactive isotope gallium, which is attracted to cancerous cells. Thus, when technicians scan images the body, they are able to pinpoint those cells.

Treatment team

Because cancer in children and adolescents is rare, young people with cancer should be referred to pediatric cancer centers with multidisciplinary teams that specialize in treating cancers in this age group. The specialty teams usually include primary care doctors, pediatric oncologists (pediatricians who specialize in the treatment of **childhood cancers**), radiation oncologists, social workers, pediatric nurses, and rehabilitation specialists.

Adult AIDS patients who develop Burkitt's lymphoma require specialists in treating HIV infection on their treatment team as well as oncologists, radiologists, and nursing specialists.

Clinical staging, treatments, and prognosis

Staging

The most common system of staging for non-Hodgkin's lymphomas in adults, including Burkitt's lymphoma, is the Ann Arbor system. It specifies four stages as follows:

- Stage I: The lymphoma is either limited to one group of lymph nodes either above or below the diaphragm, or is in an organ or part of the body other than the lymph nodes, but has not spread to other organs or lymph nodes.
- Stage II: The lymphoma is either in two or more lymph node groups on the same side of the diaphragm, or is in only one organ or site other than the lymph nodes but has spread to the lymph nodes near that organ or site.
- Stage III: The lymphoma is present in groups of lymph nodes on both sides of the diaphragm. It may involve an organ or site outside the lymph nodes, the spleen, or both.
- Stage IV: The lymphoma is disseminated (spread) throughout one or more organs outside the lymph nodes. There may or may not be involvement of lymph nodes that are remote from the affected organs.

At each stage, the patient's condition may be described in more detail by using letters to denote the presence of specific general symptoms and/or the body organs that have been affected by the disease. A is used to designate patients who do not have general symptoms; B is used for patients with any of the following:

- unexplained loss of more than 10% of body weight in the last six months
- unexplained fever higher than 38 degrees C (101 degrees F)
- drenching night sweats

The letter E is added if the patient has developed malignancies outside the lymph nodes in areas of the body other than the lymphatic system. Other sites in the body are identified with additional letters, such as D for the skin or H for the liver.

The most commonly used staging system for NHL in children is that of the St. Jude's Children's Research Hospital. It separates patients with a single tumor or diseased lymph node (Stage I) or two or more tumors or diseased lymph nodes on the same side of the diaphragm (Stage II) from those with a large chest or abdominal tumor (Stage III) or involvement of the bone marrow and central nervous system (Stage IV).

Treatment

Because of the rapid rate of tumor growth in this lymphoma, it is important to begin treatment as soon as possible after diagnosis. Bulky abdominal tumors or chest tumors are sometimes removed surgically before the patient begins **chemotherapy**.

Children with Burkitt's lymphoma are treated with chemotherapy and **radiation therapy**. The drug used most often to treat endemic Burkitt's is **cyclophosphamide** (Cytoxan), a drug that suppresses the immune system but has severe side effects. It may be given orally or intravenously. Radiation therapy is used to treat lymphomas that affect the jaw and the area around the eyes. Children with sporadic Burkitt's are treated with a short course of high-dose chemotherapy, usually cyclophosphamide in combination with **methotrexate** (MTX), **vincristine** (Oncovin), prednisone (Meticorten), and **doxorubicin** (Adriamycin). To prevent the spread of the lymphoma to the central nervous system, the patient's head and spine may be treated with radiation therapy and intrathecal methotrexate. In intrathecal chemotherapy, the drug is injected directly into the patient's spinal fluid.

Adults with sporadic Burkitt's lymphoma are treated with a combination of radiation therapy and chemotherapy. A newer high-dose chemotherapy regimen called CODOX-M/IVAC, which is a combination of cyclophosphamide, vincristine, doxorubicin, methotrexate, **ifosfamide** (Ifex), **etoposide** (VePesid), and **cytarabine** (ARA-C), appears to produce good results. Adults with AIDS are usually given low-dose chemotherapy because their immune systems are already damaged. They do not respond as well to treatment as patients without HIV infection.

Newer methods of treatment include bone marrow or stem cell transplantation and **monoclonal antibodies** (antibodies produced by cloned mouse cells grown in a laboratory). One monoclonal antibody, **rituximab** (Rituxan), has been approved by the FDA for treatment of non-Hodgkin's lymphomas, including Burkitt's lymphoma. **Clinical trials** in France indicate that rituximab combined with standard chemotherapy improves the rates of remission and survival in high-risk patients.

Prognosis

The prognosis for children with Burkitt's lymphoma is generally good, as this type of lymphoma responds well to chemotherapy. Children with African Burkitt's often show a significant improvement after only one dose of cyclophosphamide. In the United States, 80% of children treated for early-stage Burkitt's lymphoma remain free from relapse three years after treatment. The newer CODOX-M/IVAC combination chemotherapy has been credited with a cure rate above 90% in both children and adults.

The prognosis for adults depends on a number of factors. In recent years, the International Prognostic Index, or IPI, has been used to predict a specific patient's chance of recurrence and length of survival on the basis of five factors. Each of the following factors is given one point:

- age over 60 years
- the lymphoma is classified as Stage III or Stage IV
- the lymphoma has spread to more than one site outside the lymph nodes
- high levels of lactate dehydrogenase (an enzyme used to measure tumor burden)
- poor general health

An IPI score of 0 or 1 is associated with a 70% rate of disease-free survival at the end of five years and an overall survival rate of 73% at the end of five years. An IPI score of 5, on the other hand, is associated with five-year rates of 40% disease-free survival and 26% overall survival respectively.

In patients with AIDS, the factors that affect the prognosis include: the CD4 lymphocyte count; the presence of opportunistic infections (AIDS-defining ill-

nesses); involvement of the bone marrow; spread of the lymphoma beyond the lymph nodes; age; and the patient's overall strength. A history of opportunistic infections, a CD4 count below 200, age above 35, and being too weak to walk indicate a poor prognosis. The average length of survival of HIV-positive patients with Burkitt's lymphoma is six months.

Alternative and complementary therapies

Alternative and complementary treatments that have been reported as helpful to lymphoma patients include yoga, therapeutic massage, meditation, creative visualization, acupuncture, Reiki, journaling, and art therapy.

Coping with cancer treatment

Adults being treated for Burkitt's lymphoma are most likely to be affected by the side effects of chemotherapy (nausea, hair loss, etc.). Patients with AIDS have the additional concern of increased vulnerability to other AIDS-related infections (**thrush**, **pneumonia**, etc.).

Children

Children being treated for Burkitt's lymphoma share many of the concerns of children with other types of cancer, such as changes in appearance (hair loss caused by chemotherapy), continuing a normal schedule (school, sports participation), and coping with such other side effects of treatment as nausea or **fatigue**. One useful resource is the Candlelighters programs, which offer support and practical information to the parents of children with cancer.

Clinical trials

As of 2001, 39 clinical trials of treatments for AIDS-related lymphomas in adults were being conducted at research centers in the United States. Because Burkitt's lymphoma is relatively rare in children, the National Cancer Institute (NCI) requests that all children with Burkitt's (or other non-Hodgkin's lymphomas) be considered as possible subjects for clinical trials. Information about current clinical trials is available at (800) 4-CANCER or <http://www.cancernet.nci.nih.gov/trialsrch>.

Prevention

Prevention of the endemic form of Burkitt's lymphoma is complicated by the high incidence of malaria in central Africa combined with inadequate medical

KEY TERMS

Ann Arbor system—A system of tumor staging used to classify non-Hodgkin's lymphomas in adults. It specifies four stages, which can be further defined by the use of letters to identify general physical symptoms and the parts of the body affected by the lymphoma. The corresponding staging system in children is the St. Jude Children's Research Hospital system.

B cell—A type of lymphocyte that produces antibodies. Burkitt's lymphoma is a cancer of the immune system in which the B cells multiply at an extremely fast rate.

Endemic—Natural to or characteristic of a specific place. In central Africa, Burkitt's lymphoma is an endemic disease.

Epstein-Barr virus (EBV)—A type of herpesvirus (human herpesvirus 4), first identified in 1964, that causes infectious mononucleosis. It is found in most patients with the endemic form of Burkitt's lymphoma, though its role in the disease is still unclear.

International Prognostic Index (IPI)—A system for predicting the prognosis of lymphoma patients on the basis of five factors.

Intrathecal chemotherapy—A form of treatment in which the drug is injected directly into the patient's spinal fluid. It is given to prevent a lymphoma from spreading to the brain and spinal cord, or to treat one that has already spread.

Lymphatic system—The system of glands, tissues, and vessels in the body that produces lymphocytes and circulates them through the body in a clear, yellowish fluid called lymph.

Lymphocyte—A type of white blood cell involved in the production of antibodies.

Monoclonal antibody—An antibody produced in the laboratory from a cloned cell rather than in the body.

Non-Hodgkin's lymphoma (NHL)—One of two major subdivisions of lymphomas. Burkitt's lymphoma is a subcategory of NHL.

Oncogene—A gene that causes the uncontrolled cell growth characteristic of cancer.

Sporadic—Occurring in isolated or scattered instances. Burkitt's lymphoma is a sporadic disease in most countries.

Translocation—The movement of a gene or group of genes from one chromosome to another. Burkitt's lymphoma is associated with a genetic translocation.

QUESTIONS TO ASK THE DOCTOR

- Should I consider bone marrow transplant or monoclonal antibodies as treatment options?
- What are the best treatment options in case of a relapse?
- (for AIDS patients) How can I best protect myself against AIDS-related infections during chemotherapy for Burkitt's lymphoma?

care. In other countries, some risk factors associated with the sporadic form can be lowered, most particularly lifestyle behaviors that increase the risk of HIV infection. In addition, patients with Burkitt's lymphoma may want to consider genetic counseling because of the role of the C-*myc* oncogene in their disorder.

Special concerns

Patients diagnosed with Burkitt's lymphoma should be followed up at regular intervals after chemotherapy because of the possibility of long-term relapse. Follow-up examinations should include a general physical examination, a complete blood count, and radiologic examinations.

See also AIDS-related cancers; Alopecia; Chromosome rearrangements; Nausea and vomiting.

Resources

BOOKS

Beers, Mark H., MD, and Robert Berkow, MD, editors. "Hematology and Oncology." In *The Merck Manual of Diagnosis and Therapy*. Whitehouse Station, NJ: Merck Research Laboratories, 1999.

ORGANIZATIONS

American Cancer Society (ACS). 1599 Clifton Road, NE, Atlanta, GA 30329. (404) 320-3333 or (800) ACS-2345. Fax: (404) 329-7530. <http://www.cancer.org>.

Candlelighters Childhood Cancer Foundation. 7910 Woodmont Avenue, Suite 460, Bethesda, MD 20814. (301) 657-8401 or (800) 366-CCCF.

National Cancer Institute, Office of Cancer Communications. 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. TTY: (800) 332-8615. <http://www.nci.nih.gov>.

NIH National Center for Complementary and Alternative Medicine (NCCAM) Clearinghouse. P.O. Box 8218, Silver Spring, MD 20907-8218. TTY/TDY: (888) 644-6226. Fax: (301) 495-4957.

OTHER

Lymphoma Information Network. [cited June 27, 2001]. <http://www.lymphomainfo.net>.

Oncology Channel. [cited June 21, 2001]. <http://www.oncologychannel.com>.

Rebecca J. Frey, Ph.D.

Buserelin

Definition

Buserelin is a synthetic analog of natural gonadotropin-releasing hormone and is used to treat **prostate cancer**. Buserelin, also called buserelin acetate, is sold under the brand name Suprefact in Canada. It is not commercially available in the U.S. for human use.

Purpose

Androgens, particularly **testosterone**, appear to play a major role in prostate cancer. Buserelin inhibits production of luteinizing hormone from the pituitary gland which decreases the levels of testosterone. Prostate cancer is often sensitive to testosterone levels, thus, a reduction in testosterone may influence the rate of cancer growth progression and affect the size of the tumor. Hormone therapy with buserelin cannot cure prostate cancer but may decrease symptoms and improve the quality of life for most patients.

Breast cancer may also treated with buserelin. A research study examined combined treatment with buserelin and **tamoxifen** in women with premenopausal metastatic breast cancer. Together, these drugs were more effective and resulted in longer overall survival than treatment with either drug alone.

Description

Buserelin indirectly decreases the testosterone levels in the body. Testosterone is produced in the testes and the adrenal glands, but the testes will only produce testosterone if adequate levels of luteinizing hormone are present. Buserelin reduces the production of luteinizing hormone, thus causing a drop in testosterone levels. When buserelin administration is started, a brief increase in the hormone levels in the first few days or weeks may occur.

Recommended dosage

Two dosage forms of buserelin are available. Either as an injection (1 mg/mL multidose vial) or as an intranasal spray (100 mcg/spray).

A dose of 500 mcg (0.5 milligrams [mg]) is injected under the skin three times per day for seven days every eight hours. The doctor may lower the dose to 200 micrograms (mcg) or 0.2 mg once a day with time if required. Treatment with the nasal spray form of the drug is administered at 200 mcg, (2 sprays) into each nostril every eight hours. The doctor determines the duration of treatment.

Precautions

Buserelin induces a temporary rise in sex hormones at the start of treatment, but they usually remain within the normal range. This rise may be associated with an increase in disease symptoms in some patients. Symptoms such as **bone pain**, impaired urination, and muscular weakness in the legs may occur with the temporary increase in tumor activity. These symptoms usually ease gradually, although they can be avoided altogether by prescribing an antiandrogen such as cyproterone acetate or flutamide at the same time.

Due to these effects, it is advisable for patients to also take an antiandrogen with buserelin if a temporary increase in the size of the tumor may lead to: urinal tract obstruction, increased intracranial pressure (in rare cases with brain metastases), or paresis (slight or incomplete paralysis) due to increased pressure on the spinal cord. Antiandrogen treatment should be started about five days before buserelin and for three to four weeks along with buserelin therapy until the sex hormones have returned to an acceptable level.

Buserelin causes sterility in men and menopause in women which may be permanent. It is not known if buserelin is safe to use during pregnancy. Due to the secretion into breast milk, breast-feeding is not recommended. In addition, it is not known if buserelin is mutagenic or carcinogenic.

Alert doctors or dentists about buserelin therapy before receiving any treatment.

Side effects

Many people have very few side effects with buserelin, while others may experience more. The most common side effects are:

- Nasal irritation.
- Skin reaction at the injection site. The injection may be slightly uncomfortable, and redness might occur at the injection site following administration.

KEY TERMS

Androgens—A male hormone necessary for the normal sexual development of males. Some androgens are produced naturally in the body.

Antiandrogens—A drug that decreases the level of male hormones in the body. Nonsteroidal antiandrogens (eg, flutamide, bicalutamide, nilutamide) counteract the effect of testosterone within prostate cancer cells.

Luteinizing hormone—A hormone that comes from part of the brain known as the pituitary gland. The testes will only produce testosterone if adequate levels of luteinizing hormone are present.

Testosterone—A male hormone, an androgen, produced in the testes and the adrenal glands. Testosterone is responsible for many male sex characteristics such as facial hair.

Tumor—An abnormal mass of tissue that serves no purpose. Tumors may be either benign (non-cancerous) or malignant (cancerous).

- Hot flushes.
- Headache (when administered through the nasal passage).
- Burning, swelling, and/or **itching** at place of injection.
- Loss of libido and impotence during treatment.
- Breast tenderness or fullness. Slight breast swelling and tenderness may occur. This side effect can be reduced with medication.
- Weight gain.
- Fatigue.
- Depressive moods.
- Feelings of sickness and **diarrhea**. They are usually mild and controlled easily.
- Dry nose (when administered through the nasal passage).
- Tumor flare. Because buserelin may temporarily increase testosterone levels for the first few days or weeks of treatment, an increase in symptoms may be experienced. Serious disease flare reactions may occur such as an increase in bone pain, **spinal cord compression**, or urinary tract obstruction.
- Thrombosis with pulmonary embolism.
- Calcium loss in the skeleton (women).

Interactions

There are no known interactions between buserelin and any other medication reported to date.

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Busulfan

Definition

Busulfan (also known by the brand name Myleran) is a **chemotherapy** medicine used to treat cancer by destroying cancerous cells.

Purpose

Busulfan is approved by the Food and Drug Administration (FDA) to treat chronic myelogenous leukemia (also called **chronic myelocytic leukemia**). It has also been less commonly used for other acute leukemias and a blood disease known as polycythemia vera, in which there are too many red blood cells. Busulfan is also used in combination with other chemotherapy drugs for a procedure known as **bone marrow transplantation**.

Description

Busulfan a member of the group of chemotherapy drugs known as alkylating agents. Alkylating agents interfere with the genetic material (DNA) inside the cancer cells and prevent them from further dividing and producing more cancer cells. Busulfan is taken orally and comes in tablet form.

Recommended dosage

Busulfan can be taken following several different dosing schedules, depending on the disease. Busulfan is a 2mg oral tablet, and patients may need to take more than one tablet at a time depending on the dose. The induction or starting dose is 4mg up to 12mg per day. This may then be decreased to 1mg to 3mg per day as a maintenance dose. The dose of busulfan for use in combination with other chemotherapy drugs before a bone marrow transplant is much larger than leukemia dosing. Busulfan, when used for bone marrow transplants, is dosed by patient body weight. Busulfan is usually given at a dose of 4mg per kilogram of body weight each day for 4 days before a bone marrow transplant.

KEY TERMS

Anemia—A red blood cell count that is lower than normal

Bone marrow transplant—A procedure that destroys all of a patients' diseased bone marrow and replaces it with healthy bone marrow

Cataract—Formation on the lens of the eye that causes cloudy vision

Chemotherapy—Specific drugs used to treat cancer

Food and Drug Administration—A government agency that oversees public safety in relation to drugs and medical devices

Gout—A disease caused by a buildup of uric acid in the joints causing pain

Hemoglobin—A respiratory pigment in the red blood cells that combines with and transports oxygen around the body

Intravenous—To enter the body through a vein

Metastatic—Cancer that has spread to one or more parts of the body

Neutropenia—A white blood cell count that is lower than normal

Polycythemia vera—A blood disease in which too many red blood cells exist in the body

Thalassemia—A genetic form of anemia that prevents affected individuals from synthesizing hemoglobin properly

Precautions

Blood counts are monitored regularly while on busulfan therapy. During a certain period of time after receiving busulfan, there is an increased risk of contracting infections. Caution should be taken to avoid unnecessary exposure to bacteria and viruses. All patients should increase their daily fluid intake while receiving this drug.

Patients who are pregnant or are trying to become pregnant should notify their physician before taking busulfan (or any chemotherapy medication). Busulfan causes a high incidence of sterility in males, and has been known to cause sterility in females as well.

Patients with a known previous allergic reaction to chemotherapy drugs, or who suffer from gout, thalassemia, or seizure problems, should notify their physician before beginning treatment. The physician should also be consulted before receiving live virus **vaccines** while on chemotherapy.

Side effects

The most common side effect expected from taking busulfan is low blood counts, referred to as **myelosuppression**. Lowering of the white count, or **neutropenia**, is common and lasts for some time before the white count returns to normal levels. When the white blood cell count is low, patients are at an increased risk of developing a **fever** and infections. The platelet blood count can also be decreased due to busulfan administration. Platelets are blood cells in the body that cause clots to form; the purpose of these clots is to control bleeding. When the platelet count is low, patients are at an increased risk for both bruising and bleeding. If the platelet count remains too low, a platelet blood transfusion may be an option for treatment. Busulfan also causes low red blood cell counts, or **anemia**. Low red counts make patients feel tired, dizzy, and fatigued. **Erythropoietin** is a drug that can be used to increase red blood cell count.

In bone marrow transplant patients, the dose of busulfan that is given in combination with other chemotherapy drugs is intended to cause complete bone marrow destruction prior to bone marrow transplant.

Nausea, vomiting, loss of appetite, mouth sores, and **diarrhea** are rare side effects from busulfan at normal doses, but are common at the higher doses used for bone marrow transplant. If **nausea and vomiting** are a problem, patients can be given medications known as **antiemetics** before receiving busulfan to help prevent or decrease these side effects. Taking busulfan on an empty stomach may also decrease nausea and vomiting.

Damage to nerves and nervous system tissues is uncommon with standard busulfan therapy. However, at high doses, some reports do exist of seizures, dizziness, confusion, and visual disturbances.

Busulfan can also cause severe lung problems known as ''busulfan lung''. Symptoms include a nonstop cough, shortness of breath, fever, and difficulty breathing.

Less common side effects caused by busulfan include skin rashes or reactions (including darkening of the skin), dryness of the skin, **itching**, and hair loss (**alopecia**).

Although it is uncommon, severe liver problems may occur due to busulfan administration at higher doses. Rare reactions to busulfan include: lung problems, cataracts, fatigue, heart problems, low blood pressure, development of another type of cancer or leukemia, enlarged breast tissue (referred to as gynecomastia), and increased uric acid levels (which can lead to kidney problems and gout).

Any side effects experienced by a patient should be reported to his or her physician.

Interactions

Busulfan used for transplant purposes, when given in high doses with the chemotherapy drug **cyclophosphamide**, caused an increase in serious heart problems.

Patients who have taken busulfan with the drug **thioguanine** over long periods of time have shown an increase in enlarged veins in the esophagus and liver problems.

Nancy J. Beaulieu, RPh., BCOP

C

Calcitonin

Definition

Calcitonin is a hormone involved in regulating calcium metabolism. The hormone calcitonin is produced by the thyroid gland. A synthetic human product, sold as Calcimar or Miacalcin, is available in the United States. A third brand called Fortical applied for U.S. Food and Drug Administration (FDA) approval in 2003 for marketing in the United States.

Purpose

Calcitonin is often ordered for cancer patients experiencing **bone pain** due to **metastasis**. Calcitonin is also used to treat Paget's disease, post-menopausal osteoporosis, and increased levels of calcium in the blood.

Description

Calcitonin reduces breakdown of bone. It causes less bone tissue to be reabsorbed. It slows the rate of bone destruction and decreases the amount of calcium released into the blood. Most calcitonin ordered for patients is derived from salmon. Calcitonin is not effective when given orally, and is available for injection or in a nasal spray.

Recommended dosage

The usual dose for patients receiving calcitonin-salmon for bone metastases is 200 IU given through the vein twice daily. It is important to take this drug exactly as ordered. If a dose is missed and is noticed within two hours, the drug should be taken. If it is not noted until later, the patient should skip the dose and return to the regular schedule. Patients should not take additional or double doses. When using calcitonin to lower calcium levels, therapy is limited to approximately five days. Extended use of calcitonin results in a loss of calcium-lowering effect.

Precautions

Calcitonin-salmon solution should be stored in the refrigerator, not frozen. Patients should allow a new bottle of nasal spray to warm to room temperature. It may be kept at room temperature for two to four weeks. The nasal spray pump should be primed before using. Patients should push the plunger until a mist is observed, usually within several pushes. Before using, the patient should blow his or her nose. The patient should alternate nostrils with each dose. The head should be kept upright. The pump should be pressed toward the bottle one time. The patient should not inhale when spraying. The patient should then inhale through the nose and exhale through the mouth. The nosepiece should be wiped clean after each use. Patients giving themselves an injection should check that the contents are clear. Patients should not inject medication that is colored or grainy.

Calcitonin should be used cautiously when breast feeding, as it may decrease the amount of available milk. Its use during pregnancy has not been adequately studied. However, animal studies indicated a risk for low birth weight offspring.

Side effects

Calcitonin is a protein. It may cause a severe allergic reaction. The doctor should be notified if a rash or hives develop. Patients should have supplies on hand to manage an allergic reaction. Skin testing may be done prior to treatment. Allergic reactions are rarer in the human product than in the salmon product.

Diarrhea, red skin, poor appetite, nausea, vomiting, stomach pain, and back and joint pain are common side effects. Other side effects include increased or decreased appetite, gas, constipation, or an unusual taste in the mouth. Nausea is usually mild and temporary. Giving calcitonin at bedtime may decrease **nausea and vomiting**. Patients may experience dizziness, difficulty sleeping, anxiety, headache, agitation, palpitations, or

KEY TERMS

Paget's disease—Chronic inflammation of the bone, with the bones becoming thinner and softer. Long bones bow.

Osteoporosis—Disease causing bone tissue to become brittle.

other heart problems. Redness, swelling and soreness may occur at the injection site. Patients using the nasal spray may develop crusting or patches in the nose, as well as nasal dryness, redness, swelling or irritation. Less often, those using the nasal spray may experience difficulty with urination, breathing problems, loss of smell, or cold symptoms. Some patients injecting the drug may develop frequent urination, chills, dizziness, headache, chest pressure, a congested nose, tingling or discomfort in the hands and feet, difficulty breathing or weakness. Patients should notify the doctor if side effects occur. Side effects may subside as the patient's body becomes accustomed to the drug. Patients should receive regular medical checks and lab work to assess for adverse reactions and changes in urine content.

Interactions

At present, there are no known interactions with other drugs.

Resources

PERIODICALS

Boersig, Charles."Nasal Calcitonin in Greece." *Med Ad News* November 2003: 14.

Debra Wood, R.N.
Teresa G. Odle

Cancer biology

Definition

Cancer is the second leading cause of death in the United States, with one out of every three Americans falling victim to it at some point in their lives. It is a disease of unregulated cell growth. The knowledge gained in cancer biology over the past 20 years has allowed for the discovery of new, highly targeted drugs to treat cancer.

Causes of cancer

The molecular cause of cancer involves mutations in the nuclear DNA (the genetic material in cells) that can be caused by chemicals, viruses, radiation or spontaneous mutations. Although much importance has been put on chemicals and environmental pollutants as carcinogens (agents that cause cancer), it actually turns out that the predominant factors in determining cancer are associated with lifestyle. For instance, cigarette smoking accounts for 30% of cancers in males. Dietary factors are associated with another 35% of all human cancers. It is estimated that with dietary improvements there could be a 50% reduction in colon and rectal cancers, a 25% reduction in **breast cancer** and 15% reductions each in prostate, endometrial and gallbladder cancers. Other cancers that might be decreased by dietary improvements include cancer of the stomach, esophagus, pancreas, ovaries, liver, lung and urinary bladder. This adds up to 9% reduction in overall deaths. It is estimated that if Americans doubled their intake of fruits and vegetables and fiber and decreased their fat intake by 25%, significant advances could be made. Obesity also puts an individual at an increased risk of death for uterus, gallbladder, kidney, stomach, colon, and breast cancers. Obese women have a 55% greater risk of mortality from cancer than women of normal weight, while men are at a 33% greater risk of mortality. Alcohol and lack of exercise are also associated with increased risk for cancer.

Cell growth

Normal growth of cells is a highly regulated cellular function. The stimulus to begin cell division comes from growth factors that react with growth factor receptors on the surface of the cell. After the binding of growth factor to a growth factor receptor, the growth message is carried from the surface of the cell to the nucleus through a cascade of biochemical reactions referred to as signal transduction. Once the signal reaches the nucleus, transcription factors bind to the DNA, which turns on the production of proteins involved in growth and division of the cells.

DNA contains genetic information that encodes proteins involved in all aspects of cell metabolism. If a gene is damaged or mutated, the protein it encodes will be affected. DNA mutations can result in an altered expression of protein; either too much or too little, or in altered forms of a protein that either do not perform their function or perform it differently. Damage to genes that encode for proteins regulating cell growth such as oncogenes, tumor suppressor genes and DNA repair genes can result in alterations in cell growth and thus cancer.

Oncogenes

Oncogenes are altered forms of normal genes called proto-oncogenes. There have been over 100 oncogenes identified so far. Their primary role in the cell is in regulation of growth. They encode growth factors, growth factor receptors, transcription factors that regulate the manufacturing of new proteins and signal transduction proteins. Signal transduction refers to the process of transmitting a signal from the outside layer of the cell, through the cytoplasm into the nucleus of the cell and begins with a growth factor and receptor interaction. Cancer cells sometimes have altered levels of growth factors or their receptors or factors involved in signal transduction. For example, the K-*ras* oncogene is an example of a mutated signal transduction protein involved in cancers such as colon and lung cancer, and the HER2/neu oncogene is a mutated receptor associated with breast cancer. Finally, this series of biochemical reactions reaches the nucleus to affect gene transcription, or the reading of genes into RNA and protein. This occurs via transcription factors. Mutations in transcription factors result in abnormal levels of certain proteins that can result in cancer. *Myc* is an example of a transcription factor mutated in lung cancer.

Tumor suppressor genes

Also called anti-oncogenes, tumor suppressor genes code for proteins that halt cell growth. In the normal cell, when DNA has become damaged, the cell stops growing to devote time to repairing DNA. Factors responsible for allowing this repair to take place are tumor suppressor genes. If tumor suppressor genes malfunction, the cells do not stop dividing when DNA is damaged and the mutation is then carried over to the daughter cells after cell division. This increases the risk of developing cancer. In hereditary cancers it is often a malfunctioning tumor suppressor gene that is inherited. Although there are two copies of each tumor suppressor gene, the second gene can take over the role if it is not mutated. A mutation in the second copy of the gene is required for total loss of tumor suppressor function. There are dozens of tumor suppressor genes identified that are involved in cancer including p53 (identified with many cancers) and APC in **colon cancer**, and BRCA-1 in breast cancer.

Characteristics of cancer cells

Cancer cells appear differently than normal cells do under the microscope. Their nucleus is much larger than in normal cells, their chromosomes are irregular in distribution and the nucleoli in the nucleus are very prominent. When cancer cells are grown in culture in the lab they also appear different than normal cells. Rather than growing in neat single-layer sheets with one next to the other they grow more haphazardly. They have long processes that extend from the cells, they overlap one another and their shape is more rounded. Normal cells will continue to divide and grow in a culture plate until they touch a neighboring cell where they receive a signal to stop growing. Cancer cells, on the other hand, do not receive this signal and grow on top of each other forming piles of growing cells that resemble a tumor.

Normal cells require growth factors added to their growth medium to enable them to grow in culture. Cancer cells do not require the same amount of growth factors, possibly because they are able make their own growth factors. Normal human cells will grow for a short amount of time in culture and then die, while cancer cells tend to keep on growing. The term given for this ability is immortalization. Cancer cells in culture are immortalized or have unlimited growth potential.

Cancer cells also have a more immature appearance compared to normal cells. This is referred to as dedifferentiation, or they lack differentiation. As an embryo matures and develops, its cells differentiate. This means they take on more specific roles that are reflected in their appearance—kidney cells begin to look different than skin cells or breast cells. Cancer cells look less and less like the tissue they are part of and more like embryonic cells. They also produce embryonic proteins that are used as **tumor markers** such as carcinoembryonic antigen (CEA) and alpha fetoprotein (AFP).

Pathology

Tumors are either malignant or benign depending upon their invasiveness. Benign tumors are less aggressive, less likely to invade the surrounding tissue, less likely to metastasize (spread) and are slower growing. Although it sounds as if they pose no threat to the individual, this is not always the case. A tumor in the brain especially can be life threatening and put pressure on the brain as it grows. A benign tumor may also secrete hormones that in high levels can be toxic to the individual.

A malignant tumor is more aggressive, more invasive into the surrounding tissue, faster growing and more likely to metastasize. Malignant tumors usually kill the individual if they are not removed. The diagnosis as to whether a tumor is benign or malignant is done on a small sample of the tumor, called a **biopsy**. A pathologist will microscopically examine a thin, stained slice of the tissue. The tumor is graded, or given a number from 1 - 4 that corresponds to its degree of malignancy, with 4 being the most malignant and 1 being benign. The more malignant the tumor, the less organized the cells of the tissue are and the more anaplastic or dedifferentiated they appear.

The tumor is also staged which refers to the amount it has spread. This is done both by gross examination of the patient and by microscopic examination of the tissue. The staging relates to the patient's prognosis. The best prognosis is if the tumor is confined to the epithelial layer of an organ and not spread into the basement membrane. The prognosis is worse if the tumor cells have spread to adjacent lymph nodes. As a tumor grows, it becomes capable of both invasion and **metastasis**.

An organ of the body consists of epithelial cells that are supported by a basement membrane. (Epithelial cells are cells that form the tissue that covers internal and external surfaces of the body and is found on skin and mucosal surfaces.) The basement membranes separate the epithelial cells from connective tissues that are rich in blood vessels. As the tumor enlarges, it can grow into the surrounding tissue, through the basement membrane and into blood or lymph vessels. This is a critical point in the growth of a tumor. Now, a small piece of tumor can break off and travel through the circulation until it receives a signal to attach to the vessel wall. It can then move through the vessel, into the tissue bed, where it grows to become a secondary tumor. This is termed metastasis. Two common locations for metastasizing tumors are the lungs and the liver.

Cancer can also involve the immune system and individuals with weakened immune systems are often at increased risk for developing cancer. AIDS patients, for example, are at increased risk for developing some cancers, such as **Kaposi's sarcoma**. As a cell becomes cancerous, it develops different antigens on its cell surface that should be recognized by the immune system and removed. For some reason, the immune system does not remove tumors. Probably, many cancer cells do develop in the body that are identified and removed by the immune system. It is not understood why this happens occasionally but not consistently. There have been documented cases of spontaneous tumor regression which may be due to activation of the immune system.

These unique antigens expressed on the surface of cancer cells can be used to the patient's advantage in treating cancer. **Monoclonal antibodies** are proteins produced in the laboratory from a single clone of a B cell, the type of cells of the immune system that make antibodies. Antibodies, also known as immunoglobulins, are proteins that help identify foreign substances to the immune system, such as bacteria or a virus. Antibodies work by binding to the foreign substance to mark it as foreign. The substance that the antibody binds to is called an antigen. Monoclonal antibodies that can recognize and attach to the specific antigens found on cancer cells are now being used to target cancer cells directly.

Unfortunately, cancer may go undiagnosed until it is quite advanced. This is because the body has many ways to adapt itself to damage and so symptoms are reduced for some time. Metastasis may be present by the time cancer is diagnosed. Symptoms of cancer include pain emanating from the organ being stretched, as well as **fever** and weakness. As the disease progresses, cachexia (the wasting that occurs due to starvation and debilitation caused by the cancer) may occur. The patient becomes unable to mount an anti-inflammatory response and infections occur. These infections become the cause of death in most cancer patients.

Carcinogenesis

How does a cancer cell become a cancer cell? Most scientists agree that cancer is a "multi-hit" process—a process that requires a series of genetic mutations that occur either spontaneously, are inherited or are caused by specific carcinogens. There are several stages in the development of cancer: initiation, promotion and progression.

- Initiation. During initiation, a carcinogen interacts with and damages the DNA. Repair can occur after this point and the process can be reversed.
- Promotion. Promotion causes reproduction or proliferation of these damaged cells, forming a mass of cells or a benign **adenoma**. This stage is still reversible and removal of the promoting agent can stop the expansion of the tumor mass.
- Progression. Progression, however, is irreversible and involves a number of sequential mutations in genes including oncogenes and tumor suppressor genes. The end result of progression is a late adenoma that eventually converts to a malignant carcinoma. This entire process can take 20 years or more.

A specific multistep **carcinogenesis** scheme has been outlined for colon cancer that involves the following sequence of events:

- mutation of the APC tumor suppressor gene causing loss of its function
- activation of the K-*ras* oncogene
- loss of function of the DCC ("Deleted for Colon Cancer") tumor suppressor gene followed by loss of function of the p53 tumor suppressor gene Such defining of the process of carcinogenesis can identify tumor markers used for diagnosis and monitoring of cancers. Also, an understanding of pathways involved in carcinogenesis can provide information to better design and target drugs, making them more specific to decrease their effects on normal cells.

Information gained on carcinogenesis pathways can also be used to research targets for gene replacement therapy.

Angiogenesis

As the tumor grows, its need for a blood supply increases. A tumor larger than 1 mm diameter (0.03 in) cannot continue to grow without access to circulation. Blood supplies the nutrients the tumor requires and can remove the toxic metabolites that are built up in the tumor tissue. To keep up with the demand for blood vessels, the tumor releases factors called angiogenic factors. One such factor is termed vascular endothelial growth factor (VEGF). These factors initiate the growth of more blood vessels into the tumor. This process of increased blood vessel growth is termed angiogenesis. The rich supply of blood vessels also gives the tumor more opportunity to metastasize to distant sites by traveling through the blood. Using drugs that can block angiogenesis is a newly developing field of cancer treatment.

Apoptosis

Apoptosis is a way the organism has of removing genetically damaged cells from itself to prevent cancer. It is different from another process of death called necrosis where damaged tissue dies for various reasons. When DNA damage occurs to the cell, the body has many opportunities to repair this damage and thus to prevent cancer. If the DNA repair does not occur, however, the last chance the organism has to protect itself from cancer is to eradicate the entire cell. This programmed cell death, or selective destruction of a cell, is called apoptosis. Precancerous cells receive signals that activate this self-destruct program. Genes that are involved in apoptosis include bcl-2 (breast cancer tumor suppressor genes 1 and 2) and p53. When these genes are mutated, apoptosis is limited and the risk of a cell becoming cancerous is increased. Some anti-cancer drugs act by stimulating the apoptotic pathway.

Tumor markers

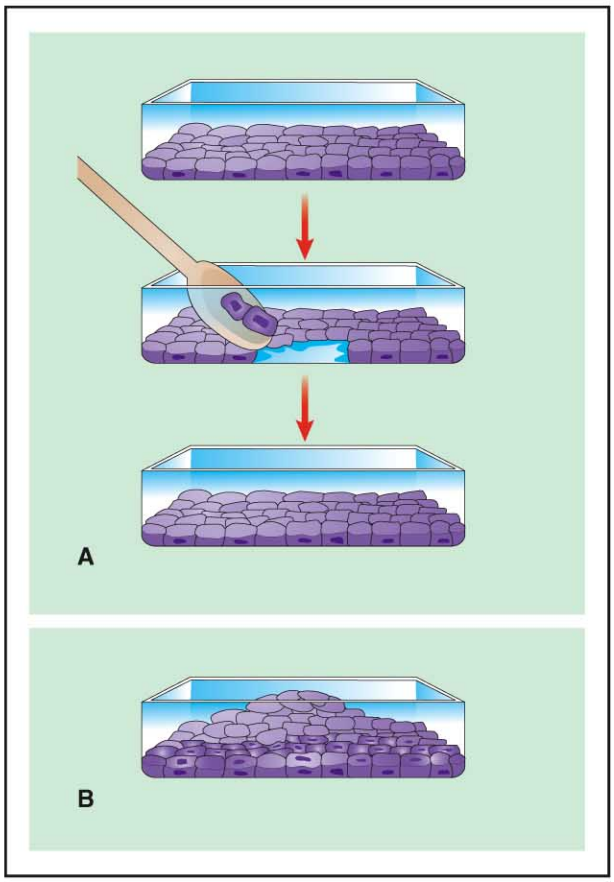
Tumor markers may be soluble factors secreted by cancer cells, altered proteins retained by cancer cells, or mutated genes in the cancer cells. They are typically identified in the blood of patients but sometimes tissue from a biopsy is necessary. Tumor markers can be used as an aid in diagnosing cancer but, more importantly, they can give information on the prognosis of the cancer and aid the clinician in determining appropriate treatment. For instance, if the tumor marker HER-2/neu associated with breast cancer is identified in a patient, specific **chemotherapy** that is directly targeted to the HER-2/neu protein can be used giving the patient a better prognosis. Some tumors secrete high levels of hormones that are used as tumor markers to help identify the cancer. For instance, choriocarcinoma (a malignancy that originates inside the uterus) produces large amounts of human chorionic gonadotropin (hCG). The presence of hCG in the blood helps identify the tumor. Other common tumor markers include prostate-specific antigen associated with **prostate cancer** and CA 125 associated with **ovarian cancer**.

Genetics

Cancer is basically thought of as a genetic disease. (That is not to say, however, that all cancers are inherited.) Genes are sequences of DNA located on chromosomes within the nucleus. The genes contain information that encodes proteins involved in all aspects of cell metabolism. Genes involved in cell growth and division are the most important in regards to cancer. These genes are oncogenes, tumor suppressor genes and DNA repair genes. Before science had the ability to identify specific genes it was noted that some cancers were associated with chromosomal abnormalities. For instance, chronic myeloid leukemia (CML) is associated with a fragmented chromosome termed the Philadelphia chromosome. The Philadelphia chromosome results from a translocation of part of chromosome 22 to chromosome 9. Using newer molecular techniques, we now know that this translocation results in a fusion between two oncogenes: *bcr* and *abl*.

We now know of many hereditary conditions that result in an increased risk of cancer. Although hereditary cancers are actually quite rare, they are notable because individuals who inherit a predisposition for cancer become afflicted with cancer at a much earlier age than those without an inherited susceptibility. Cancer results from a series of genetic mutations that may take 20 years or more to accumulate. If one of these mutations is inherited, it shortens the time for cancer to develop. Individuals with hereditary predispositions tend to get cancer at a much earlier age than those who get non-hereditary cancer.

Familial colon cancer and breast cancer are two widely known examples of inherited cancers. One percent of individuals with colon cancer has an inherited condition called familial adenomatous polyposis (FAP). Individuals with FAP inherit a mutation of the adenomatous polyposis coli (APC) gene, a tumor suppressor gene that is involved in apoptosis. Patients with FAP tend to have many benign polyps of the colon and are likely to develop colon cancer by the age of 40. Mutation of the APC gene is an early event in non-hereditary colon



A. When normal cells in a culture plate are scraped away, the cells on the plate divide to replace them. The cells on the plate grow until they touch a neighboring cell and receive a signal to stop growing. B. Cancer cells do not receive this signal and grow on top of each other, forming piles of cells, or tumors. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*

cancer as well. The difference is that in non-hereditary colon cancer, this mutation is a spontaneous event, and the accumulation of mutations that result in cancer occur later in life than with hereditary colon cancer.

There are two genes associated with hereditary breast cancer, the BRCA1 gene and the BRCA2 gene. About 80% of families with cases of early onset breast cancer have mutations in the BRCA1 gene. This gene is also associated with increased risk of ovarian cancer. The BRCA2 gene, associated with hereditary breast cancer, is related to ovarian cancer to a lesser extent than BRCA1. Both genes act as tumor suppressor genes.

The **Li-Fraumeni syndrome** is a hereditary syndrome that puts individuals at an increased risk for a number of cancers including breast cancer, soft tissue **sarcomas**, osteosarcomas, brain tumors, leukemias and adrenocortical carcinomas. Individuals with this syndrome have mutations in the tumor suppressor gene, p53. Mutations in this gene are associated with 50% of all cancers. The protein associated with p53 is found in the nucleus of the cell and regulates cell functions such as cell cycle, DNA repair, and apoptosis. Mutations in p53 are also noted in colon cancer.

Other hereditary cancer syndromes include **retinoblastoma** in which a mutated Rb gene is inherited and neurofibromatosis in which a mutated NF1 gene is inherited. The K-*ras* gene is an oncogene that is commonly mutated in many types of cancer including colon and lung cancer. Individuals who are part of families with high rates of these types of cancers can choose to be genetically tested to determine if they are at an elevated risk for developing cancer.

Treatment

Most cancer treatments center around three modalities, surgical removal of the tumor, radiotherapy, and chemotherapy to kill the cancer cells. If the cancer has not spread and is isolated, surgery is the best option as it can physically remove the entire tumor. The location of all tumor tissue must be able to be identified for this procedure, however. There are risks of surgery that include those associated with anesthesia and infection.

Radiation therapy uses x rays directed at the tumor to cause damage that kills the cells. Radiation therapy will also affect normal tissue that lies in the radiation field. These side effects will vary depending upon the part of the body undergoing treatment.

Chemotherapy involves using drugs that circulate through the body to affect the tumor. The first drugs that were used to treat cancer are the antimetabolite drugs such as **methotrexate** and **mercaptopurine**. These drugs were designed to interfere in cell division and kill rapidly dividing cells. Unfortunately, they cannot differentiate between rapidly dividing tumor cells and rapidly dividing normal cells. The toxic effects on non-tumor cells account for many of the side effects of chemotherapy, including loss of hair and gastrointestinal problems. Calculating the correct dosage of these drugs is very important to minimize side effects. Although these drugs cause more side effects because they are delivered to the entire body, this is the only way to treat tumors that have metastasized from the main tumor.

Knowledge gained about cancer over the past 20 years or so have brought about cancer therapies more directly targeted at proteins known to be involved in carcinogenesis. For instance, small molecules that can specifically inhibit signal transduction proteins can slow cancer growth. A new drug known as **imatinib mesylate** (formerly known as STI-571) deactivates the enzyme

called tyrosine kinase, which allows the growth of **chronic myelocytic leukemia** cells.

Monoclonal antibodies can be made in the lab that are able to recognize specific antigens on cancer cells. These antibodies can in turn be joined to cancer drugs and be used to deliver the drug directly to the cancer cell. Being able to deliver the cytotoxic drug to the cancer cell decreases the side effects on normal tissue.

New categories of cancer treatment have also evolved including hormone therapy and immunotherapy, also called biological therapy or biological response modifiers. Biological therapy takes advantage of the body's own immune system to recognize the cancer and remove it. Cytokines are immunoregulatory substances secreted by the cells of the immune system. Immunotherapy can use cytokines that are naturally produced by the body and affect immune cells and blood cells. These cytokines include **interferons**, interleukins and colony stimulating factors, such as **filgrastim** and **sargramostim**. For instance, interferon-alpha and interleukin-2 are now used to treat metastatic **melanoma**.

Hormonal treatment of cancer aims to interfere with some hormonal action on cancer cells. This therapy is mostly used on breast cancer and prostate cancer. Some breast cancers grow in response to estrogen. The anti-estrogen **tamoxifen** can reduce the amount of growth in breast cancer. Prostate cancer grows in response to **testosterone**. Drugs can be used to decrease the amount of testosterone produced by the testes.

Finally, gene therapy has potential to directly target genetic abnormalities found in cancer cells. The tumor suppressor protein p53 is found mutated in a large number of cancers. By introducing the appropriate DNA sequence into a cell, this protein can be replaced bringing back the ability of the cancer cell to undergo apoptosis.

Tumor growth

A tumor that can be clinically identified is typically at least one gram in size and has undergone 30 population doublings. It is before this point that tumor growth has been its fastest and now growth has slowed down significantly. This growth curve of cancer is expressed mathematically by the Gompertzian equation. According to this growth curve, most tumors originate two years before detection. Why does tumor cell growth slow down after it reaches the one-gram size? Factors that contribute to this decline in growth include lack of oxygen, decreased availability of nutrients, accumulation of toxic metabolites and lack of communication between cells.

KEY TERMS

Anaplastic—The undifferentiated appearance common to a cancer cell.

Antisense—An RNA sequence that can prevent the synthesis of a specific protein.

Chromosomes—Structures within the nucleus of the cell that contain DNA.

Genome—All the genetic information of an organism.

Immortal—To grow and divide indefinitely.

Metastasis—Cancer growth at a secondary site.

Nucleus—The cellular compartment containing the chromosomes.

Nucleoli—Structures within the nucleus of the cell that are associated with chromosomes.

Phenotype—The physical expression of the DNA, or the appearance of an organism.

Understanding the Gompertzian growth curve mathematics can help with decisions about cancer treatment. Most chemotherapy drugs target fast-growing cells and so they work best when a tumor is growing quickly. If at the time a tumor is detected, its cells are growing slower, then chemotherapy is less effective. If initial treatment involves surgery or radiation therapy, then the number of tumor cells will be decreased enough that cells will begin to reproduce again at a faster rate of growth. This makes chemotherapy more effective following surgery or radiation therapy to reduce the tumor load. This might also explain why some patients seem to go into remission only to have their cancer recur later. During remission, the cell number was too low to be detected, but cell growth was rapid during that period.

Many times a patient's response to chemotherapy is very good only to be followed by a relapse with a drug-resistant tumor. Combination chemotherapy, or the use of more than one drug at a time, is often more effective that single drug therapy. This is because cancer cells can spontaneously mutate and become resistant to drugs. This ability to mutate was mathematically explained by Goldie and Coldman and named the Goldie-Coldman model. This model predicts that spontaneous mutations in cancer cells that are capable of leading to **drug resistance** occur every 10,000 to 1,000,000 cell divisions. Basically this model implies that smaller tumors are less likely to be drug-resistant and are easier to cure. By treating tumors early and aggressively, the chance of recurrence with a

drug-resistant cancer decreases. The combination of active drugs is also more effective in reducing the initial cancer.

This model of combination chemotherapy has proven useful in treating childhood **acute lymphocytic leukemia**, **Hodgkin's disease**, and **testicular cancer**. However, it has not proven useful in treating some solid tumors. These tumors seem to have a much higher capacity to develop drug resistance. The drugs used to treat these cancers are actually capable themselves of promoting resistance in the tumors. Resistance to one of these drugs often results in resistance to another drug and is referred to as multi-drug resistance. Multi-drug resistance is due to a decreased uptake and increased elimination of the drugs from the tumor cells. A specific pump has been identified in cancer cells that is responsible for multi-drug resistance.

Resources

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American Cancer Society. 1599 Clifton Road NE, Atlanta, GA, 30329. (800) 227-2345. <http://www.cancer.org>.

American Society of Clinical Oncology. 225 Reinekers Lane, Suite 650, Alexandria, VA 22314. (703) 299-0150. <http://www.asco.org>.

National Cancer Institute. 9000 Rockville Pike, Building 31, Bethesda, MD 20892.(800) 4-CANCER. <http://www.nci.nih.gov>.

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Cindy L. A. Jones, Ph.D.

Cancer cluster

Definition

The National Cancer Institute (NCI) defines a cancer cluster as "the occurrence of a greater than expected number of cases of [cancer] within a group of people, a geographical area, or a period of time." Cancer is not the only disease that sometimes occurs in clusters; AIDS, SARS, and certain types of food poisoning are other examples.

Cancer clusters are also defined by a primary cancer of a specific tissue or organ; cases involving metastases to that part of the body are not included in evaluations of suspected clusters.

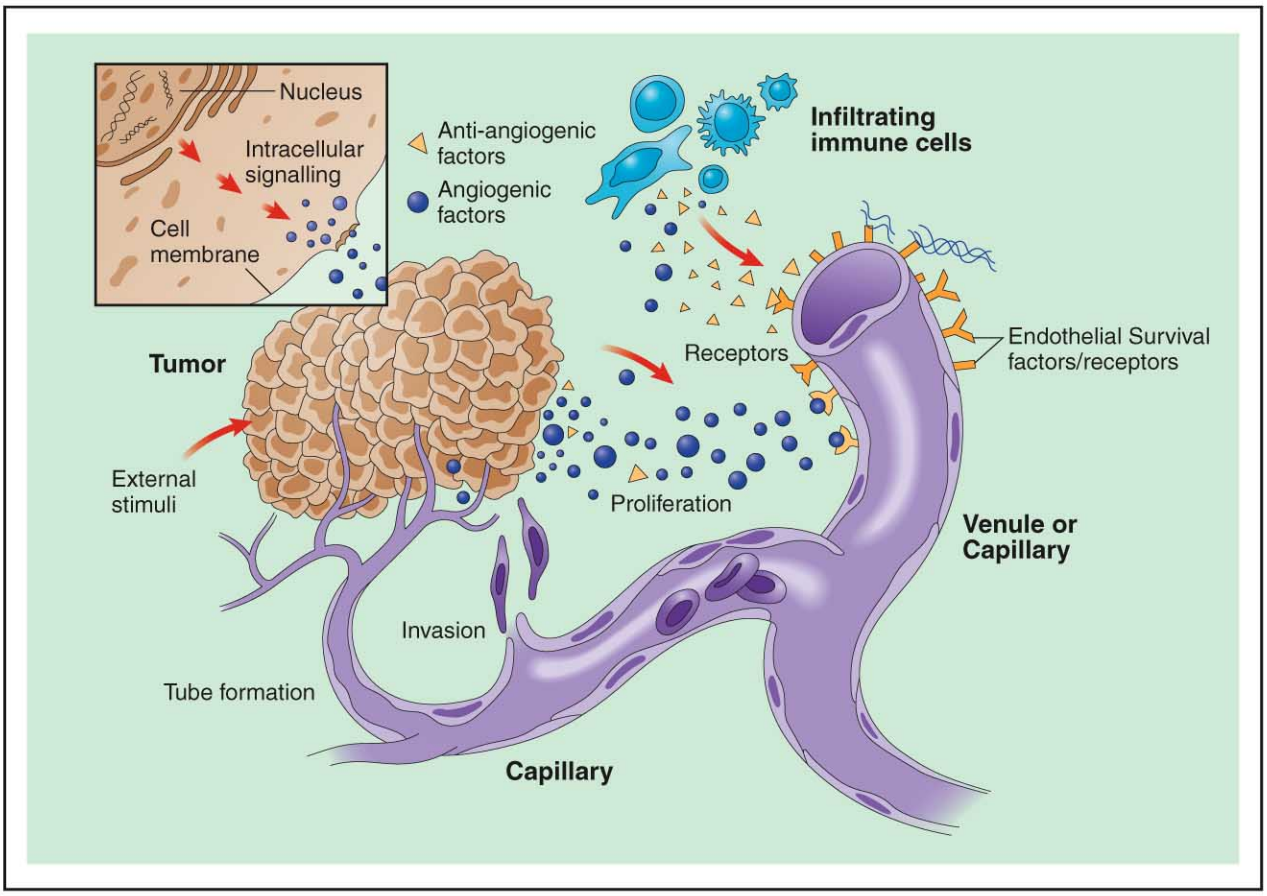
Description

Although some cancer clusters have received considerable publicity through books and films about their investigation, they are much less common than many people think. Epidemiologists and toxicologists in the United States receive about 1500 requests every year to investigate suspected clusters; however, very few of these turn out to be genuine clusters. A suspected cluster has a greater chance of being a true cluster when all of the following factors are present:

- All the reported cases of cancer belong to one type or closely related types.
- The cancer is an uncommon type.
- The type of cancer affects members of a group that does not usually develop this form of cancer, as when young people develop a type of cancer usually seen in the elderly.

There are several reasons why it is hard to prove that a group of cancer cases is a true cluster:

- Cancer is not a single disease but a term that covers over a hundred different diseases, each with its own set of causes, risk factors, demographic patterns, and characteristic symptoms.
- The causes of cancer include a variety of external and internal factors ranging from chemicals or radiation in the environment to inherited genetic mutations and hormone levels in the body. Lifestyle differences (occupation, nutritional status, use of tobacco and alcohol, etc.) and racial and ethnic differences also affect an individual's risk of developing cancer. All these risk factors and environmental exposures interact in complex ways that are not fully understood as of the early 2000s.
- Cancer takes a relatively long time to develop, often ten years or even longer following exposure to an environmental trigger.



Angiogenesis. To keep up with the demand for blood vessels, the tumor releases factors called angiogenic factors. (An individual tumor cell is shown in the inset.) These factors initiate the growth of more blood vessels into the tumor. The rich supply of blood vessels also gives the tumor more opportunity to metastasize (spread) to distant sites by traveling through the blood. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*

- Many reported clusters involve only a small number of cases, which complicates statistical analysis. Another way of putting the problem is that a relatively small number of cases makes it harder to exclude the possibility of simple chance or coincidence.
- It is not always easy for doctors to determine the **primary site** of a patient's cancer, which in turn makes it hard to decide whether the patient should be counted as part of a cancer cluster.
- The so-called "sharpshooter's fallacy." Sharpshooter's fallacy refers to a story about a man who fires a gun at random into a target and then draws a circle around the bullet holes, thus creating the appearance of a bulls-eye that does not really exist. In investigating a suspected cancer cluster, some observers tend to expand the geographical boundaries of the cluster to include new cases as they appear, thus creating the illusion of a cancer cluster. This particular fallacy was involved in the theory—which was publicized in the mid-1990s by articles in the *New Yorker* and other popular magazines—that exposure to the electromagnetic fields surrounding high-voltage power lines causes cancer clusters in neighborhoods around the transmission towers.

Causes

As cancer is not a contagious disease, true cancer clusters result from a combination of genetic factors that increase some individuals' susceptibility to specific types of cancer, combined with exposure to environmental carcinogens. Environmental factors known to be related to cancer include sunlight and other forms of radiation as well as toxic chemicals and atmospheric pollutants.

Special concerns

Possible clusters of cancers that primarily affect children are given priority by public health investigators. It is noteworthy that two well-known cases concerned childhood leukemia—the cluster of cases in Woburn,

Factors that favor the progression of cancer

Genetic susceptibility
Age
Mutations
Abnormal cell growth
Aneuploidy (abnormal numbers of chromosomes)
Growth and survival factors
Angiogenesis
Loss of heterozygosity (Having only one version of a gene instead of the usual two different versions)
Gene amplification

Factors that help to protect the body from cancer

Genetic resistance
Nutrition
Metabolism
DNA repair
Tumor suppressor genes
Cell differentiation
Death of damaged tissue
Programmed cell death
Immune system

Massachusetts, in the 1970s, and a newer cluster first reported in 1999 in Churchill County, Nevada. The Bureau of Environmental Health Assessment (BEHA) of the Commonwealth of Massachusetts maintains a frequently updated website about the Woburn cluster. The Nevada cluster is still under investigation as of early 2005.

Reporting a cancer cluster

Prior to 1990, the Centers for Disease Control and Prevention (CDC) had primary responsibility for investigating suspected cancer clusters. Since that date, departments of public health at the state or local level have conducted initial evaluations of cancer clusters. Persons who think there may be a cancer cluster in their neighborhood or workplace should first contact their local health department or their state's cancer registry. Contact information for state health departments and cancer registries is available through the CDC website. The CDC and such other national agencies as the National Center for Environmental Health (NCEH) and the National Institute of Environmental Health Sciences (NIEHS) will join the investigation if the state health department requests their help.

Investigating a cancer cluster

When a possible cancer cluster is reported, the state health department will take the following steps:

- Ask the person reporting the cluster for information about the type of cancer involved, number of cases, suspected time period or geographic area, etc. Information will also be requested about each case in the cluster (patient's contact information, the length of time they have lived in the area, etc.) and diagnostic information about the cancer (patient's age at diagnosis, whether the cancer is primary or metastatic, etc.) Between 75 and 80 percent of reports are closed at this point because the basic information indicates that the group of cases is not a true cluster.
- If the cluster seems to require a closer look, the investigators will contact the patients to verify diagnoses and obtain medical records; compare the number of cases with information from cancer registries and data banks to determine whether the cluster represents an unusually high rate of occurrence; and consult the relevant medical literature for reports of possible occupational or environmental factors linked to the type of cancer.
- If necessary, the state health department will contact the CDC and other federal agencies to help conduct a comprehensive study. Fewer than 4 percent of reported clusters are investigated at this level.

Interested readers may wish to test their own skills in medical investigation by playing a game called "Cluster Busters," listed under Resources below. The game, which can be downloaded from the NIEHS website, was originally developed to teach health sciences students at the University of Arizona.

Interpreting the findings

If a comprehensive investigation does indicate that a reported cancer cluster is a true cluster, this finding does not necessarily mean that the cases resulted from one single risk factor or environmental cause. The investigators may arrive at any of the following conclusions:

- The cluster resulted from chance.
- The expected number of cancer cases in the group of people defined as being at risk was calculated incorrectly.
- The cancers have a known cause (such as smoking).
- The cancers have a cause that is still unknown.

See also Leukemia.

Resources

BOOKS

Harr, Jonathan. *A Civil Action.* New York: Vintage Books, 1996. The classic book-length account of the cluster of childhood leukemia cases in Woburn, Massachusetts, and the court case that grew out of the medical investigation.

KEY TERMS

Carcinogen—Any substance that causes cancer.

Epidemiology—The branch of medicine concerned with studying outbreaks of disease in large groups of people, the factors that affect the frequency or spread of disease, and detection of the sources or causes of epidemics.

Toxicology—The branch of medicine concerned with the effects of poisonous substances and treatment of these effects. Toxicologists are often involved in investigations of cancer clusters.

PERIODICALS

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Cancer genetics

Definition

Cancer genetics is the study of the process in which multiple alterations occur in genes that the changes in cells that leads to cancer. Cancerous cells continuously divide and change, leading to uncontrolled division and proliferation (duplication) of cells. These genetic alterations are referred to as mutations, which are changes in the normal DNA sequence of a particular gene. Mutations may include deletions, chromosomal translocations, inversions, amplifications, or point mutations.

Cancer genetics is the understanding of the genetic processes underlying the actual disease occurrence. This understanding plays a significant role in early detection, therapy, prevention, and prognosis.

Description

Nearly all cancers originate from a single cell and are the result of genetic alterations, although most of them are not inherited. Individuals who are genetically predisposed to a particular cancer will not necessarily develop the disease in the absence of somatic mutations. Somatic mutations occur in non–sex determining cells, meaning they will not be passed on to offspring. These mutations can be influenced by environment and other causes, such as an individual's habits (i.e. smoking). A single genetic error or mutation in a cell does not typically cause malignancy; instead it develops after a series of mutations over a period of time.

Regulation of cell death and survival

A balance between cell division and death of the old, degenerated cells is essential for proper cellular functioning of any organism. Cells that can no longer duplicate or that have sustained injuries (like hypoxia, heat, extreme cold, or ultraviolet radiation) are candidates for cell death. Alternatively, cells can be killed if infected by intracellular organisms (pathogens), or damaged cells may be engulfed by a host's lymphocytes (white blood cells involved in cellular defense mechanisms). Another form of cell death in the disease process is a suicide mechanism initiated by cells known as apoptosis. In this process, extracellular or intracellular signals may trigger the degradation of nuclear material resulting in cell death. Some of the apoptotic genes like bcl2 family members (bcl-X, A1, bax, bad) are likely involved in various cancers. Studies to alter the activity of bcl2 family members and related genes will be of potential use in designing cancer therapies.

Oncogenes and tumor suppressor genes

The constant cell proliferation in cancer may either be due to over-activation of a specific gene that promotes cell division or the improper functioning of a gene that will otherwise restrain growth. Genes that promote cell division are proto-oncogenes—positive regulators of cell division. Overexpression of proto-oncogenes results in uncontrolled cell growth. Genes that suppress or restrain growth are tumor suppressor genes. Loss of their function results in unregulated cell division. An alteration in the function of genes in each of these classes is due to a change, or mutation, in the DNA within the cell. The different types of mutations include point mutations, amplifications, and chromosomal alterations.

Point mutations

DNA is composed of a string of nucleotides, each containing a phosphate group, deoxyribose, and one of four bases; adenine (A), guanine (G), cytosine (C), and thymine (T). These bases are paired as either A-T or C-G and the pairs compose the "rungs" in the double helix structure of DNA. The order of the bases creates the genetic code for development. A sample genetic code is CAG-TAA-CCA-GCG, etc. These triplets code for synthesis of specific proteins.

A point mutation is a single nucleotide change in a DNA strand. This may alter the genetic code, thus altering the function of the protein. In the above example, a point mutation in the thymine base of the second triplet would look like: CAG-AAA-CCA-GCG. Changing the code from TAA to AAA could alter the function of a protein and thus could cause a predisposition to disease such as cancer. One example of a point mutation that has been identified is the *ras* family of oncogenes (such as H*ras*, K-*ras*, N-*ras*), present in 15% of all human cancers.

Childhood cancers associated with congenital syndromes or malformations

Syndrome or Anomaly	Tumor
Aniridia	Wilms' tumor
Hemihypertrophy	Wilms' tumor Hepatoblastoma Adrenocortical carcinoma
Genito-urinary abnormalities (including undescended testicles)	Wilms' tumor Ewing's sarcoma Nephroblastoma Testicular cancer
Beckwith–Wiedmann syndrome	Wilms' tumor Neuroblastoma Adrenocortical carcinoma
Dysplastic nevus syndrome	Melanoma
Nevoid basal cell carcinoma syndrome	Basal cell carcinoma Medulloblastoma Rhabdomyosarcoma
Poland syndrome	Leukemia
Trisomy-21 (Down syndrome)	Leukemia Retinoblastoma
Bloom syndrome	Leukemia, gastrointestinal carcinoma
Severe combined immune deficiency disease	EBV-associated B-lymphocyte lymphoma/leukemia
Wiscott-Aldridge syndrome	EBV-associated B-lymphocyte lymphoma
Ataxia telangiectasia	EBV-associated B-lymphocyte lymphoma Gastric carcinoma (stomach cancer)
Retinoblastoma	Wilms' tumor Osteosarcoma Ewing's sarcoma
Fanconi anemia	Leukemia Squamous cell carcinoma
Multiple endocrine neoplasia syndromes (MEN I, II, III)	Adenomas of islet cells, pituitary, parathyroids, and adrenal glands Submucosal neuromas of the tongue, lips, eyelids Pheochromocytomas Medullary carcinoma of the thyroid (thyroid cancer, a specific type) Malignant schwannoma Non-appendiceal carcinoid
Neurofibromatosis (von Reckling hausen syndrome)	Rhabdomyosarcoma Fibrosarcoma Pheochromocytomas Optic glioma Meningioma

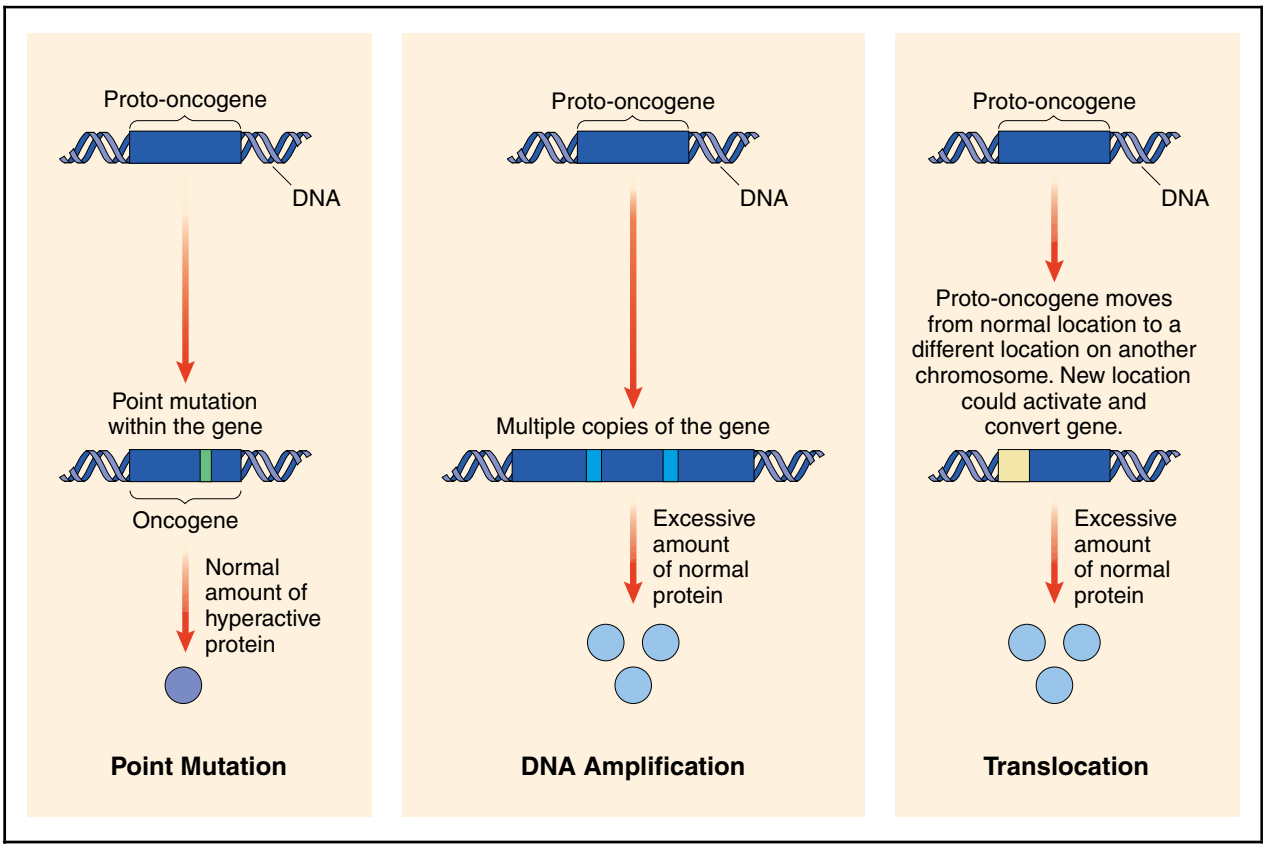
DNA amplification

Another mechanism of oncogene activation—DNA amplification—results in an increase in the amount of DNA in the cell. A large number of genes are amplified in human cancers.

DNA amplification can be detected by cytological staining (a method in which the amplified DNA is stained), or by another fluorescent technique called comparative genomic hybridization (CGH). CGH allows the specific recognition of regions of gene amplifications in tumor DNA and is a more sensitive diagnostic tool.

Chromosomal alteration

Chromosomal alteration may involve translocations and is often seen in lymphoid tumors. Translocation is the transfer of one part of a chromosome to another chromosome during cell division and may involve transcription factors (i.e., nuclear factors), signal transduction proteins, and cellular regulatory molecules.



Point mutation, DNA amplification, and chromosomal alterations (like translocations) are three examples of mutations that can turn proto-oncogenes into oncogenes. *(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)*

DNA repair genes

In addition to oncogenes and tumor suppressor genes, DNA repair genes may lead to cancer. DNA repair genes are capable of correcting the errors that occur during cell division. Malfunction of these repair genes, either through inherited mutation or acquired mutation, may affect cell division resulting in malignancies.

RNA and DNA viruses

Malignancies are known to be associated with RNA or DNA viruses. A retrovirus is an RNA virus that possesses a single-stranded RNA as its genetic material, in contrast to the double-stranded DNA. Retroviruses are known to induce malignancies in animals, and one known human malignancy is T-cell **lymphoma** or leukemia caused by human T-cell lymphotropic virus (HTLV) type I.

DNA viruses are implicated in human malignancies more often than RNA viruses. **Human papilloma virus** is related to human **cervical cancer**, and hepatitis B and C are related to hepatocellular carcinoma (liver cancer). In addition, the **Epstein-Barr virus** that causes the commonly known infectious mononucleosis also causes **Burkitt's lymphoma** in Africa and nasopharyngeal carcinoma in parts of Asia.

Mendelian cancer syndromes

Some forms of cancer are classified as hereditary cancers, or familial cancers, because they follow the Mendelian pattern of inheritance, the more familiar form of inheritance in which genetic material is passed from the mother or father to the offspring during reproduction. Cancer-related genes may be inherited as autosomal dominant, autosomal recessive, or x-linked traits.

About 100 syndromes have been identified as hereditary cancers although not all of them are common. Some of the known tumor suppressor genes responsible for **familial cancer syndromes** are *BRCA1*, which is associated with breast, ovarian, colon, or prostate cancers; *BRCA2* involved in **breast cancer**, male breast cancer, and **ovarian cancer**; *TSC2* associated with angiofibroma; and *RB* associated with **retinoblastoma** and **osteosarcoma**. The discovery of these genes that are associated with hereditary cancer syndromes is also beneficial in understanding the normal control of cell growth.

Complex inherited cancer syndromes

Several types of cancer do not follow a simple Mendelian pattern of inheritance. In many instances, environmental factors can affect the outcome of disease expression in conjunction with genetic alterations. One such example is lung cancer. Cigarette smoke is an environmental factor that may result in lung cancer for individuals frequently exposed to the toxins in the smoke. However, individuals who possess a gene that predisposed them to lung cancer are genetically more susceptible than the rest of the population to these toxins, and may develop cancer with less exposure or none at all. Individuals without a predisposing gene may not develop the cancer as readily.

It is estimated that less than 10% of breast and ovarian cancers are the result of mutations in the *BRCA1* or *BRCA2* genes. The remaining 90% of breast cancer incidences are not usually dependent on inherited factors, although family history should be investigated.

Genetic mapping and research

In 2002, researchers completed the first draft of the Human Genome Project. The project undertook identifying all of the genes in the human body. By identifying and scientifically mapping our genetic code, scientists can better explore causes, treatments, and perhaps vaccines for diseases such as cancer. Since the project was completed, rapid developments have occurred in identifying chromosomes on genes responsible for various diseases. For example, in 2003, scientists discovered a third breast cancer gene called EMSY. Late in 2003, scientists announced that measurement of new genes at diagnosis of acute lymphoblastic leukemia in children, made possible by the Human Genome Project, may help predict their outcome. Researchers have introduced a urine-based genetic test for prostate cancer. Scientists have been pushing for a tumor classification system to be added to the current cancer staging system that would be based on genetics.

Genetic counseling

Genetic counselors comprehend the medical aspects of hereditary cancer syndromes and can educate the affected family regarding available management options. Counselors communicate the risk for disease development to individuals and their families and actively participate in guiding the course of action from an unbiased perspective. Genetic counselors also aid in providing updated information regarding **genetic testing** for cancer risk, especially with the discovery of hereditary cancer–associated genes. Genetic counseling efforts may involve a team of health professionals anchored by the genetic counselor which includes a medical geneticist with appropriate background, mental health professional, a physician specializing in cancer (oncologist), and a surgeon (if the type of cancer requires surgery).

Chromosomes and cancer

Cancer type	Associated gene mutation
Chronic myelocytic leukemia	translocation resulting in the Philadelphia chromosome (Ph^1
Burkitt's lymphoma	translocation involving the c-*myc* proto-oncogene
Retinoblastoma	mutation in chromosome 13; mutation can be inherited
Wilms' tumor	mutation in chromosome 11; mutation can be inherited
Colon cancer (occurs sporadically, but also occurs as a familial cancer syndrome)	mutation in adenomatous polyposis coli (APC) gene followed by further mutations
Breast cancer (occurs sporadically and also as a familial cancer syndrome)	mutation affecting the gene *BRCA1*, or mutation in *BRCA2*

Genetic testing

Genetic testing examines the genetic information contained inside an individual's DNA, to determine if that person has a certain disease, is at risk to develop a certain disease, or could pass a genetic alteration to his or her offspring. Individuals who seek genetic testing are usually family members believed to have a predisposition or susceptibility to cancer as known from the personal family medical history. The identification of genes associated with certain types of cancers such as *BRCA1*, *BRCA2*, *HNPCC* (**colon cancer**), and *RB* improves the accuracy of DNA testing to predict cancer risk.

Often a positive test result indicates that the individual carries the abnormal gene and is more likely to get the disease for which the test was performed than the rest of the population. A negative test result can signify the absence of the abnormal gene and a lesser chance of developing the disease. However, a negative test result cannot guarantee that the person will never develop cancer at any point in his or her lifetime. This is because many mutations are induced by environmental factors and accumulate over a period of time.

It is necessary for the individual undergoing genetic testing to know that assessing the mutations is challenging and false-positive results are possible. False-positive results are those that indicate the presence of an abnormal gene that may not really exist, or the abnormal gene may result in a disorder other

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two copies of an abnormal gene must be present to display the trait or disease.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Hypoxia—Lack of oxygen to the cells that may lead to cell injury and ultimately cell death.

Infectious mononucleosis—A common viral infection caused by Epstein-Barr virus with symptoms of sore throat, fever, and fatigue. This infection is not in any way related to cancer.

Malignant—A tumor that tends to spread to local or distant tissues, usually cancerous.

Nucleotides—Building blocks of genes, which are arranged in specific order and quantity.

Oncogene—Genes that allow the uncontrolled division and proliferation of cells that lead to tumor formation and usually to cancer.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

X-linked traits—Genetic conditions associated with mutations in genes on the X chromosome. A male carrying such a mutation will contract the disorder associated with it because he carries only one X chromosome. A female carrying a mutation on just one X chromosome, with a normal gene on the other chromosome, will not be affected by the disease.

than the one for which the testing was performed. If the tests administered are not sensitive and specific, they may detect sequence variations that could be benign variants rather than the disease-causing mutations.

Genetic testing is recommended for individuals at higher risk of cancer based on the family medical history.

Genetic testing also is performed for individuals who have survived cancer at an earlier time in their lives. It may be performed to determine one or more of the following:

- risk to offspring
- necessity of prophylactic surgery in appropriate cases
- surveillance purposes
- personal cancer etiology (cause of disease)

Genetic counseling professionals can assist in the decision to perform genetic testing and in understanding the associated risks. Some individuals find it difficult to cope with the knowledge of their own genetic predisposition. These patients should consider addressing these issues with appropriate health care professionals.

See also Cancer biology; Carcinogenesis; Chromosome rearrangements.

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Cancer prevention

Definition

Preventing the incidence of cancer is complex and involves many factors that ultimately work by avoiding or limiting exposure to carcinogens. Known carcinogens in humans include physical, chemical, viral, and bacterial carcinogens. Physical carcinogens include the hydrocarbon byproducts of cigarette smoke, radiation, and asbestos. Benzene and vinyl chloride are examples of chemical carcinogens. The human papillomaviruses, which play a role in the development of **cervical cancer**, are viral carcinogens. A bacterial carcinogen is the bacteria, *Helicobacter pylori*, which has been linked to the cancer B-cell **lymphoma**, unique to the gastric mucosa. Familial (hereditary) **carcinogenesis** plays a role in as many as 15% of all human cancers and has been implicated as the cause of some cases of **melanoma**, breast, colon, and other cancers.

Some factors that place individuals at high risk for the development of cancer can be modified to decrease risk for development. For example, people can make lifestyle and environmental changes to decrease risk. Behavior modification such as dietary changes, exercise, and avoiding exposure to known carcinogens are primary prevention measures that everyone should adopt.

An evolving field, **chemoprevention**, is the use of **vitamins** or medicines to prevent cancer development. In 2003, the U.S. Preventive Services Task Force released a report stating that evidence was insufficient to recommend for or against use of vitamin supplements to help prevent cancer. The task force recommended against supplementation with beta carotene because of higher incidence of lung cancer among those who used certain levels of beta carotene supplements.

Chemopreventive agents have the ability to potentially delay and even reverse the sequence of events at the cellular level that change a normal cell to a cancer cell. An example of a chemopreventive agent is **tamoxifen**, a drug that is effective in preventing **breast cancer** in women who are at high risk for developing breast cancer. **Vaccines** for Hepatitis B virus will not only prevent primary Hepatitis B and liver failure, but also liver cancer.

Preventive surgery may be an option for those individuals who are considered to be at high risk of developing cancer because of a genetic or inherited predisposition. Examples of preventive surgery are prophylactic (preventive) **mastectomy** to reduce risk for breast cancer, and colon polyp removal in individuals at high risk for the development of **colon cancer**.

In 2003 the American Cancer Society (ACS) estimated that 30,000 cancer deaths were caused by cigarette smoking alone and some 180,000 deaths could be attributed to tobacco use. All cancers caused by smoking **cigarettes** and by excessive use of alcohol can be completely prevented. **Alcohol consumption** is another risk factor for cancer. According to the ACS, up to one-third of the more than 555,000 cancer deaths in the United States in 2003 were related to poor nutrition or insufficient physical exercise. A 2003 study reported that women of average weight who walked briskly at least 1 and one-fourth hours per week had a 30% lower risk of breast cancer than women who did not exercise. Many of the more than one million skin cancers that develop annually could be prevented by adopting protective measures from ultraviolet radiation caused by the sun.

Different cancers are associated with different risk factors. While modification of risk factors plays an important role in the prevention of cancer, it is known that some individuals who have one or more risk factors never develop cancer. Others, however, who have no known risk factors, are eventually diagnosed with cancer. Research aimed at identifying additional risk factors for specific cancers continues.

Lifestyle and cancer

Nutrition

The relationship between food intake and cancer is complex and not well understood. Research seems to indicate that certain foods may have either protective or promoting effects on the development of cancer. Foods that have a protective effect seem to play a role in the prevention of certain types of cancers. Foods that have promoting effects are associated with an increased risk of developing certain types of cancers. According to the American Cancer Society, the single most important dietary intervention to lower risk for cancer is eating five or more servings of fruits and vegetables daily. Adopting a diet rich in plant sources provides phytochemicals that possess health protective benefits. Dietary recommendations related to reducing risk of cancer include the recommendation to choose most foods from plant sources such as fruits and vegetables. Five or more servings of fruits and vegetables should be consumed every day. Fruits and vegetables should be eaten at every meal and as snacks. Other foods from plant sources that should be included in the diet several times a day include breads, cereals, grain products (preferably whole grain), rice, and pasta. Beans should be eaten as an alternative to meat. The foods and herbs with the highest anticancer activity include garlic, soybeans, cabbage, ginger, licorice root, and the umbelliferous vegetables such as

carrots. Citrus foods also contain a host of active phytochemicals.

A diet rich in foods from plant sources may reduce the risk for development of cancers of the gastrointestinal tract, respiratory tract, and colon. Vegetables that seem to play a strong role in protecting against colon cancer include green and dark yellow vegetables, vegetables in the cabbage family, soy products, and legumes. Increased consumption of fruits and vegetables reduce risk for lung cancer, even for those individuals who smoke. Forms of fruits and vegetables that appear to provide the greatest protection include foods in fresh, frozen, canned, dried, or juice forms. Extractions from fruits and vegetable do not provide protective effects.

Diets high in fat have been associated with some increased risk for colon, rectal, prostate, and endometrial (uterine) cancers. The association between high-fat diets and the development of breast cancer is much weaker. Specific dietary recommendations are to replace high-fat foods with fruits and vegetables, eat smaller portions of high-fat foods, and limit consumption of meats, especially those that are considered high in fat.

Foods from animal sources remain a staple in American diets. Consumption of meat, especially red meats such as beef, pork, and lamb, have been associated with increased risk of colon and **prostate cancer**. Cooking methods also have been linked to the development of cancer. Mutagenic compounds are produced when proteins such as meat protein are cooked at high temperatures. These compounds may be responsible for the association between meat consumption and increased risk for colon cancer.

Obesity has been linked to cancers at several sites including colon and rectum, prostate, and kidney, as well as endometrial and breast cancer in postmenopausal women.

Physical activity

Recommendations related to physical exercise include engaging in moderate levels of activity for at least 30 minutes most days of the week. Studies have revealed an association between physical activity and a reduced risk of the development of certain types of cancers, including colon, breast, and prostate cancer. For example, physical activity is thought to stimulate the movement of stool through the bowel, resulting in less exposure of the bowel lining to mutagens in the stool.

Consumption of alcohol

Drinking alcohol has been linked to increased risk of developing cancers of the mouth, esophagus, pharynx, larynx, and liver in both men and women, and increases the risk of breast cancer in women. Cancer risk increases as the amount of alcohol consumed increases. An individual who both smokes and drinks alcohol greatly increases the risk of developing cancer when compared to either smoking or drinking alone. Risk increases significantly for cancers of the mouth, esophagus, and larynx when more than two drinks per day are consumed. A drink is defined as 5 ounces (141.75 grams) of wine, 12 ounces (340.20 grams) of regular beer, or 1.5 ounces (42.52 grams) of 80-proof distilled spirits. Women who drink are at increased risk for the development of breast cancer. Studies have shown that the risk of breast cancer increases with just a few drinks per week.

Consumption of tobacco

Smoking-related illnesses account for more than 400,000 deaths each year in the United States. These deaths occur 12 years earlier than would be expected on average. Tobacco is known as one of the most potent human carcinogens. Tobacco causes more than 148,000 deaths each year in the form of various cancers. Most of the cancers of the lung, trachea, bronchus, larynx, pharynx, oral cavity, and esophagus diagnosed each year are caused by tobacco. Smoking is also associated with cancers of the pancreas, kidney, bladder, and cervix. Smoking is known to affect the health of nonsmokers through environmental or secondhand smoke, which is implicated in causing lung cancer. Cigarette smoking is more common among men; however, because of the increase in the number of women who smoke, more women die from lung cancer each year than from breast cancer. Mortality from lung cancer for men appears to have peaked and has been declining since the 1980s. This decline in mortality is attributed to a decrease in tobacco product use among men.

Substantial health benefits occur once an individual stops smoking. If a smoker stops smoking before the age of 50 years, his or her risk of dying in the next 15 years is half of that for a continuing smoker. Even if the smoker stops smoking after the age of 70 years, the risk of dying is still reduced substantially. After 10 years of not smoking, an ex-smoker's risk of lung cancer is reduced by 30%–50%. After five years of not smoking, an ex-smoker's risk of oral and **esophageal cancer** is reduced by 50%. Risk for cervical and **bladder cancer** is also reduced once smoking is stopped.

The three treatment elements identified as particularly effective in **smoking cessation** treatment include pharmacotherapy, such as nicotine replacement patches and gums, social support from physicians and other clinicians, and skills training and problem solving,

KEY TERMS

Carcinogens—Cancer-causing agents.

Gastric mucosa—Lining of the stomach.

Legumes—Foods such as peas and beans.

Mutagens/mutagenic—Capable of causing changes or mutations at the chromosome or gene level.

Umbelliferous vegetables—Vegetables from the carrot family.

particularly in the areas of smoking cessation and abstinence techniques.

Radiation exposure

Only high-frequency radiation such as ionizing radiation (IR) and ultraviolet (UV) radiation has been proven to cause cancer in humans. A source of ultraviolet radiation is sunlight. Prolonged, unprotected exposure to UV radiation is the major cause of basal and squamous cell skin cancers. UV radiation is also a major cause of melanoma. Disruption of the earth's ozone layer by pollution is thought to result in increasing levels of UV radiation reaching the earth's surface, which has been linked to the rise in the incidence of skin cancers and melanomas.

IR has cancer-causing capability as proven by studies on atomic bomb survivors and other groups. Virtually any part of the body can be affected by IR, but the areas most affected are the bone marrow and the thyroid gland. IR is released in very low levels from diagnostic equipment such as medical and dental X-ray equipment. Much higher levels of IR are released from machines delivering **radiation therapy**. Great precautions are taken during treatment not to expose patients or staff unnecessarily to the effects of IR. Another occupational group affected by IR includes uranium miners. Exposure to radon, a naturally occurring gas which is a form of IR, can increase risk for lung cancer, especially among smokers.

See also Antioxidants; Familial cancer syndromes; Occupational exposures and cancer.

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Capecitabine

Definition

Capecitabine (brand name Xeloda) is a drug that interferes with the growth of cancer cells.

Purpose

Capecitabine is used to treat **breast cancer** and cancer of the colon and rectum (colorectal cancer) that have spread to other parts of the body (metastasized).

Description

Capecitabine is a recently developed drug. It is a type of medicine called an antimetabolite because it interferes with the metabolism and growth of cells. Capecitabine is an unusual anti-cancer drug in that it is most active in cancer cells; normal cells are exposed to far lower concentrations of the drug. Cancer cells convert capecitabine into another anti-cancer drug called 5-fluorouracil (**fluorouracil**). This substance prevents cells from growing and reproducing by interfering with the production of DNA and RNA. Eventually the cells die.

Capecitabine has been approved by the U.S. Food and Drug Administration for the treatment of metastasized breast cancer that is resistant to standard **chemotherapy**. Capecitabine may be used in combination with the drug

docetaxel (Taxotere). A study completed in 2003 found that the combination of docetaxel and capecitabine improves survival in women with metastatic breast cancer without a significant increase in treatment-related side effects.

A study completed in 2001 found that capecitabine is as effective as 5-fluorouracil for treating metastasized colorectal cancer, and has fewer and less severe side effects. However, it does not increase the average survival time of approximately 13 months.

Recommended dosage

The dosage of capecitabine depends on a number of factors including body size. The average dosage is 2500 mg per square meter of body surface area per day. Capecitabine is a pill that is taken with water within 30 minutes after a meal. It may be taken every 12 or 24 hours. For colorectal cancer, capecitabine may be administered for two weeks, followed by one week off, for a total of 30 weeks.

Precautions

Capecitabine can temporarily reduce the number of white blood cells, thus reducing the body's ability to fight infection. It is very important to avoid exposure to infections and to receive prompt medical treatment if exposed. Immunizations (vaccinations) should be avoided during or after treatment with capecitabine. It also is important to avoid contact with individuals who have recently taken an oral polio vaccine.

Capecitabine may temporarily reduce the number of blood platelets that are necessary for blood clotting. The risk of bleeding may be reduced by:

- using caution when cleaning teeth
- avoiding dental work
- avoiding cuts, bruises, or other injuries

Capecitabine can cause birth defects and fetal death in animals. Therefore, this drug should not be taken by pregnant women or by either a man or woman at the time of conception. Because capecitabine may cause serious side effects, women usually are advised against breast-feeding while taking this drug.

Some individuals may have an allergic reaction to capecitabine. Allergies to foods, preservatives, or dyes, or to the drug 5-fluorouracil must be considered before this drug is prescribed.

Side effects

Common side effects of capecitabine may include:

- loss of appetite (**anorexia**
- **diarrhea**
- **nausea and vomiting**
- stomach or abdominal pain
- swelling, peeling, redness, or blistering of hands and feet
- numbness, pain, **itching**, or tingling in hands and feet
- pain, swelling, or sores in the mouth or on the lips
- rashes or dry skin
- fatigue or weakness due to reduced red blood cell countThe treatment is stopped if side effects are severe enough to interfere with eating or other normal activities.

Less common or rare side effects of capecitabine may include:

- constipation
- cough or hoarseness
- difficulty swallowing
- shortness of breath
- chest pain
- blood pressure changes
- fast or irregular heartbeat
- pain or swelling of the ankles, legs, or stomach
- poor coordination, dizziness
- changes in fingernails or toenails
- headache
- heartburn
- sensitivity to sunlight
- muscle pain
- eye irritation
- insomnia
- lower back or side pain
- painful or difficult urination

Side effects of capecitabine may include symptoms of infection, such as **fever**, chills, sore throat, or swollen glands, or symptoms of liver malfunction. Side effects also may include unusual bleeding or bruising due to the reduction in blood platelets.

Other diseases or medical conditions may increase the side effects associated with capecitabine. Chicken pox or shingles (**Herpes zoster**) may become severe and spread to other parts of the body. If heart, kidney, or liver disease is present, the side effects related to these organs may be more severe. In addition, in the presence of liver disease, the amount of capecitabine in the body may be higher. Individuals over the age of 80 often experience more severe side effects with capecitabine.

KEY TERMS

Colorectal cancer—Cancer of the colon and rectum.

Metastasis—Spread of cancer from its point of origin to other parts of the body.

Platelet—Blood component that aids in clotting.

Interactions

Other drugs that may interact with capecitabine include:

- Amphotericin B (Fungizone)
- Antithyroid drugs that are used to treat an overactive thyroid
- Azathioprine (Imuran)
- Chloramphenicol (Chloromycetin)
- Colchicine
- Flucytosine (Ancobon)
- Ganciclovir (Cytovene)
- Interferon (Intron A, Roferon-A)
- Plicamycin (Mithracin)
- Zidovudine (AZT, Retrovir)

Coumadin-type anticoagulants that are used to thin the blood and medicines containing aspirin can increase the chances of bleeding. **Folic acid**, alone or in a multivitamin, may increase the side effects of capecitabine. Finally, capecitabine can increase the effects on the blood of other cancer medicines or **radiation therapy**.

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Capsaicin

Definition

Capsaicin is the active ingredient in chili peppers, the substance that gives chili and cayenne its heat. In its purified form it is a crystalline alkaloid.

Purpose

Research on the use of capsaicin for cancer patients has focused on several areas:

- its ability to decrease pain
- its potential to be carcinogenic
- any chemoprotective capacity
- any antimicrobial and detoxification properties

Description

Folk accounts of capsaicin's medicinal properties in the form of cayenne have included aiding digestion, promoting the sweating process to create cooling (for reducing a **fever**), fighting infections, and stimulating the function of the kidneys, lungs, stomach, and heart. Research on capsaicin's ability to decrease pain has been in the areas of chronic pain, arthritic pain, migraine pain, sports injuries, and neuropathic cancer pain. It appears to interfere with chemicals that facilitate pain messages to the brain. Capsaicin has a hyperemic effect, which means that it increases blood flow similar to when an area is inflamed. When applied to the skin in cream form, the area becomes red, warm, and may become slightly swollen. Many individuals experience a localized burning sensation when a cream containing capsaicin is applied to the skin. However, with repeated use, the burning sensation usually disappears, and pain relief is noted. The burning or stinging sensation may last a few weeks for some. Capsaicin appears to work through a mechanism that initially causes a hypersensitivity to pain, and then ends in pain relief.

Several clinical studies performed on the effectiveness of various formulations of capsaicin have demonstrated that a majority of patients experience a reduction in pain and few or minor side effects. Capsaicin has been reported to have an effect against *H. pylori*, and also some antimicrobial properties. It appears to protect the lining of the digestive tract from harm due to aspirin use. Capsaicin has also showed an inhibitory effect on skin **carcinogenesis** in mice and a suppression of proliferation of human cancer cells.

Early studies on capsaicin raised the concern that capsaicin could be carcinogenic. However, further studies reported that capsaicin was not carcinogenic, and in fact might have chemoprotective properties. Studies investigating its potential to promote tumor development indicate it does not have this ability.

Recommended dosage

The Physician's Desk Reference (PDR) for Herbal Medicines indicates the availability of the following dosages of cayenne:

- Capsules: 400, 445, 450, 455, and 500 mg strengths
- Cream containing 0.25% and 0.75% capsaicin
- Liquid alcohol-based extract

The average daily dose in capsule form for cayenne (capsicum annum) is 30 to 120 mg. Individuals wishing to use capsaicin should do so under the guidance of a practitioner knowledgeable about its properties, to ensure proper monitoring for any adverse reactions.

Precautions

Capsaicin's fiery nature requires some precautions to be used when handling it in its natural form or when applying it topically as a cream. Thorough hand washing after contact with it is necessary, as it can cause an intense burning or stinging sensations. Avoid any contact with mucous membranes, such as eyes or mouth, or any open wounds, until hands have been washed. Bottles storing capsaicin or cayenne should be well sealed and kept out of the light. It should not be refrigerated.

The National Cancer Institute (NCI) cautions that it is not known whether capsaicin used by a breast feeding mother will pass into the breast milk. Individuals who have had an allergic reaction to hot peppers should speak to their health care provider before using capsaicin. Some individuals may experience a prolonged burning sensation with topical capsaicin. However, the NCI states that reducing the number of doses per day will not result in decreasing the sensation, and may prolong the time period over which the sensation is experienced. In addition, a reduction in the number of doses may also reduce the degree of pain relief. Patients taking capsaicin should not double-up on a dose if a dose is missed.

Side effects

Research on capsaicin is still in the early stages, but the following side effects have been reported:

- hypersensitivity reaction such as anaphylaxis and rhinoconjunctivitis
- abnormal blood clotting ability
- an increase in bowel function, leading to diarrhea
- blister formation on the skin
- contact dermatitis
- increase in cough with extended exposure to chili peppers
- long-term use of high dosages can lead to kidney and liver damage, chronic gastritis, and neurotoxic effects

KEY TERMS

Alkaloid—Any of a large group of bitter-tasting alkaline substances containing nitrogen that are found in plants. Capsaicin is an example of an alkaloid.

Bioavailability—A term used in describing the amount of a medication taken that is actively available to the targeted body area. Bioavailability can be affected by factors such as the rate at which a tablet or capsule dissolves, binding products using in formulating the medication, and the person's ability to break down and use the medication.

Carcinogenic—A substance that can cause cancer to develop.

Mucositis—An inflammation of the lining of the digestive tract, often accompanied by mouth and throat lesions.

Neuropathic pain—Pain that is felt near the surface of the skin, along nerve pathways.

Neurotoxic—A substance that is harmful to the nervous system.

Interactions

If aspirin and capsicum annum extract (in the form of 100 mg of capsaicin) are taken at the same time, decreased bioavailability of aspirin may occur. This treatment may interfere with MAO inhibitors and antihypertensive therapy. As with any medication, patients should notify their physician of any prescription, over-the-counter, or herbal remedies they are taking prior to receiving treatment.

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Carbamazepine

Definition

Carbamazepine (Tegretol, Carbatrol) may be administered to cancer patients as a pain medicine.

Purpose

Carbamazepine is given to cancer patients primarily as a pain medication. The drug may, for example, be prescribed for stabbing pain that moves along a nerve. For noncancer patients, it is often used to treat epilepsy or bipolar disorder (manic-depressive illness). Carbamazepine is classified as an anticonvulsant because it is often given to control seizures.

Description

Carbamazepine suppresses some of the activities of the nerves. It does this by delaying the amount of time it takes for certain passageways in the nerves to recover after they have sent out a message.

Recommended dosage

Carbamazepine comes in several forms. There are 200 mg tablets, 100 mg chewable tablets, and a liquid containing 20 mg per milliliter that may be swallowed. There are extended-release tablets of carbamazepine containing 100, 200, or 400 mg and extended release capsules of the medication containing 200 and 300 mg.

Some authorities recommend starting with 100 to 200 mg twice a day. This strategy helps to minimize side effects. Then, the dose may be gradually increased every week. Adults may eventually receive 600 to 1200 mg a day, while 20 to 30 mg per kg of body weight per day is appropriate for children.

Side effects

Carbamazepine may exhibit side effects to the nervous system, for example, drowsiness, dizziness, blurred vision, unsteadiness, **depression**, impaired concentration, and headache. Patients should be cautious about operating machinery or performing tasks requiring alertness until tolerant of the side effects. After several weeks of treatment, these side effects may disappear. To minimize these side effects, doctors may start carbamazepine at a low dose and may recommend that it be taken before bedtime. As carbamazepine may cause stomach upset and nausea, the medicine should be taken with meals.

Effects of carbamazepine may include bone marrow suppression, which involves a low white blood cell and platelet count, but this is usually not severe. Very rarely, a dangerous **anemia** may occur during carbamazepine therapy. Blood counts should be monitored for patients using this drug. Some patients with previously diagnosed depression of the bone marrow should not be given carbamazepine.

Carbamazepine may cause birth defects and should be avoided in women who are pregnant. In addition, women sometimes develop hypersensitivity reactions to carbamazepine during pregnancy. An appropriate contraceptive method should be used while on carbamazepine. Carbamazepine can cross into breast milk and should be avoided in women who are breastfeeding. Carbamazepine may also cause rash or sensitivity to the sun.

Interactions

Carbamazepine may affect the activity of other medicines, for example, oral contraceptives, **warfarin**, theophylline, doxycycline, haloperidol, **corticosteroids**, valproate, clonazepam, ethosuximide, lamotrigine, felbamate, and thyroid hormones. Oral contraceptives may become less effective if a patient is taking carbamazepine. Some doctors recommend that the form of birth control pill be altered or that a different method of contraception be used. If **phenytoin** and phenobarbital are taken at the same time as carbamazepine, the capacity of carbamazepine to interact with additional medications may increase. Side effects may occur if a patient is taking carbamazepine and one of the following medications simultaneously: **danazol**, dextropropoxyphene, erythromycin, clarithromycin, isoniazid, verapamil, or diltiazem. Due to the numerous potential of interactions with other drugs, patients should consult with their physician or pharmacist prior to starting any new medications either bought over the counter or initiated by another physician. Patients taking carbamazepine should not drink grapefruit juice.

Carbamazepine sometimes complicates the treatment of brain tumors because it can lower the blood level of other drugs given to stop the growth of the

KEY TERMS

Anticonvulsant—A type of medication given to prevent seizures. Carbamazepine is an anticonvulsant.

Bipolar disorder—A mood disorder in which the patient experiences both periods of mania and periods of depression.

Bone marrow— The spongy tissue found in the large bones of the body.

Trigeminal neuralgia—A nerve problem associated with pain.

tumor. Researchers are currently exploring the use of newer anticonvulsant drugs in treating patients with brain tumors.

Carbamazepine has also been reported to interact with certain herbs, including evening primrose (*Oenothera biennis*), gingko (*Gingko biloba*), and wormwood (*Artemisia pontica*). Patients should always tell their doctor about any herbal preparations they may be taking as well as other prescription medications.

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Carboplatin

Definition

Carboplatin is a chemotherapeutic agent used to treat cancer by interfering with the growth of cancer cells. At the molecular level, carboplatin causes cancer cells to destroy themselves through the mechanism of apoptosis. Carboplatin is marketed under the brand name Paraplatin; it may also be referred to as CBDCA, JM-8, or carboplatinum.

Purpose

Carboplatin was approved in 1989 by the Food and Drug Administration (FDA) for the palliative treatment of **ovarian cancer**. The term palliative means that the treatment is not intended to cure but only to relieve symptoms. Carboplatin has also been used to treat other types of cancer, including head and neck cancer, **cervical cancer**, lung cancer, **endometrial cancer**, **testicular cancer**, hormone-refractory prostate cancer, and brain tumors.

More recently, carboplatin has been investigated in clinical trials as a possible treatment for squamous cell skin cancers and malignant melanoma.

Description

Carboplatin is a member of the group of **chemotherapy** drugs known as heavy metal-like alkylating agents. Alkylating agents interfere with the genetic material (deoxyribonucleic acid, or DNA) inside the cancer cells and prevent them from further dividing and growing more cancer cells.

Recommended dosage

The dose of carboplatin can be calculated using several methods. A carboplatin dose can be determined using a mathematical calculation that measures a person's body surface area (BSA). This number is dependent upon a patient's height and weight: the larger the person, the greater the body surface area. BSA is measured by the square meter (m^2). The body surface area is calculated and then multiplied by the drug dosage in milligrams per square meter (mg/m^2). This calculates the actual dose a patient is to receive.

A common dosage of carboplatin alone for the treatment of patients with recurrent ovarian cancer is 360 mg/m^2 given on day one into a vein every four weeks. When given in combination with the chemotherapeutic agent **cyclophosphamide** for the treatment of recurrent

ovarian cancer, a dose of 300 mg/m^2 administered intravenously is typical. This combination is repeated every four weeks for six cycles.

The second way to determine the dose of carboplatin is for the physician to measure or estimate how well the patient's kidneys work. The patient may be asked to collect all of their urine in a bottle for a 24-hour period. The sample will then be sent to a laboratory and analyzed. A mathematical calculation is performed to determine how well the patient's kidneys are working and subsequently to determine the carboplatin dose.

Precautions

Blood counts will be monitored regularly while on carboplatin therapy. During a certain time period after receiving carboplatin there is an increased risk of getting infections. Caution should be taken to avoid unnecessary exposure to infectious agents. Patients should also check with their doctors before receiving live virus **vaccines** while on chemotherapy.

Patients who may be pregnant or trying to become pregnant should talk to their doctor before receiving carboplatin. Men and women undergoing chemotherapy are at risk of becoming sterile.

Patients with known previous allergic reactions to chemotherapy drugs should notify their doctors.

Side effects

Most of the side effects of carboplatin are due to its induction of apoptosis in tumor cells. **Nausea and vomiting** are among the most common side effects from receiving carboplatin. Nausea and vomiting can begin up to six hours after treatment and can last as long as 24 hours. Patients are given medicines known as **antiemetics** before receiving carboplatin to help prevent or decrease this side effect. **Diarrhea**, loss of appetite, constipation, pain, and weakness have also been reported to occur.

Myelosuppression, or a suppression of bone marrow activity resulting in a low blood cell count, is expected to occur following carboplatin administration. When a patient's white blood cell count drops below normal (leukopenia), there is an increased risk of developing a **fever** and infections. Neupogen, a drug used to increase the white blood cell count, may be administered.

A decrease in platelet count is most notable following carboplatin administration. Platelets are blood cells that aid for the formation of clots. When the platelet count becomes abnormally low, patients are at an increased risk for bruising and bleeding. If the platelet count remains too low a platelet blood transfusion is an option. Low red blood cell counts (**anemia**) may also occur following many cycles of carboplatin administration; during the first cycles this is usually not a common problem. Low red blood cell counts may result in dizziness and **fatigue** and can be treated with the drug **erythropoietin**.

A less common side effect of carboplatin is damage to nerves and nervous system tissues. Patients may feel tingling and numbness of the fingers and toes. This side effect is more common in patients over 65 years of age or those who have previously received the chemotherapy drug **cisplatin**. Other less common side effects include rash, **itching**, hair loss (**alopecia**), mouth sores, hearing problems, kidney problems, liver problems, vision problems, swelling, redness and pain at the site of injection, allergic reactions, heart problems, and breathing problems.

Carboplatin may cause the body to waste certain normal electrolytes that circulate in the body. Low levels of magnesium, calcium, phosphate, or sodium can be

KEY TERMS

Anemia—An abnormally low red blood cell count.

Apoptosis—Cell self-destruction, usually brought about by irreparable damage to the cell's DNA. Carboplatin and other platinum-derived cancer drugs work by inducing apoptosis in cancer cells.

Chemotherapy—Specific drugs used to treat cancer.

DNA—Deoxyribonucleic acid; the genetic material inside of cells.

Electrolytes—Natural salt substances in the body that move in and out of cells to maintain cell function.

Food and Drug Administration (FDA)—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives the approval to pharmaceutical companies for commercial marketing of their products.

Intravenous—Entering the body through a vein.

Leukopenia—An abnormally low white blood cell count.

Metastatic—Cancer that has spread to one or more parts of the body.

Palliative—Referring to treatment intended to relieve symptoms rather than cure a disease.

found in patients who have received carboplatin. These rarely cause difficulties and are monitored by the doctor.

Some patients develop hypersensitivity or allergic reactions to carboplatin that may include difficulty breathing, rash, itching, redness in the face, dizziness, an increased heart rate, and a drop in blood pressure. The risk of such reactions is increased in patients who have had more than six cycles of treatment with the drug. A group of researchers in Ohio has developed a skin test to evaluate patients for possible hypersensitivity reactions to carboplatin, and a second team is working on a desensitization regimen that will allow patients who have become hypersensitive to the drug to continue to benefit from treatment with it.

Interactions

Patients being treated with carboplatin should avoid other drugs that may cause damage to the kidneys or hearing.

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United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA (463-6332). <http://www.fda.gov>.

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Carcinogenesis

Definition

Also called tumorigenesis, carcinogenesis is the molecular process by which cancer develops.

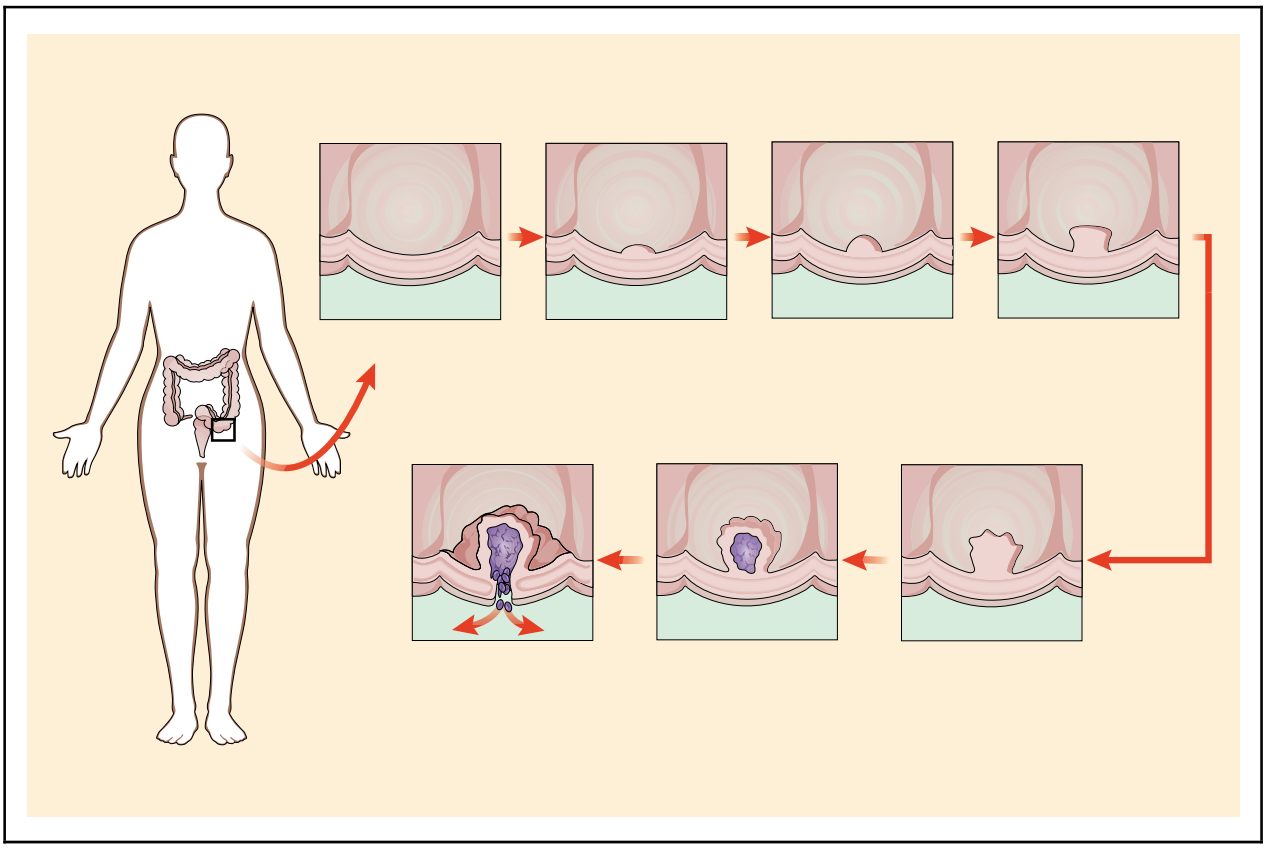
Description

The development of cancer is a complicated process in which a large number of factors interact to disrupt normal cell growth and division. Cancer can be caused by a number of internal factors such as heredity, immunology, and hormones as well as external factors such as chemicals, viruses, diet, and radiation. Although attention is often focused on environmental chemicals (such as asbestos and coal tar) as a cause of cancer, only 5% of cancers can be linked to chemical exposure. We now know that the chief causes of cancer are lifestyle factors such as diet, cigarette smoke, alcohol, and sun exposure. In fact, dietary factors are associated with 35% of all human cancers and cigarette smoke for another 30%.

Whatever the cause of cancer, its development is a multi-stage process involving damage to the genetic material of cells (deoxyribonucleic acid, or DNA). This damage occurs in genes regulating normal cell growth and division. Because several stages or several mutations are required for cancer to develop, there is usually a long latent period before cancer appears.

Carcinogens

Agents that cause cancer (carcinogens) can be classified as genotoxic or nongenotoxic (also referred to as epigenetic). Genotoxins cause irreversible genetic damage or mutations by binding to DNA. Genotoxins include chemical agents like N-methyl-N-nitrosourea (MNU) or non-chemical agents such as ultraviolet light and ionizing radiation. After the carcinogen enters the body, the body makes an attempt to eliminate it



Colon cancer has become a model for studying multi-stage carcinogenesis. Four distinct sequential mutations have been described in the development of colon cancer: mutations of the APC (adenomatous polyposis coli), K-ras, DCC (deleted in colon cancer), and p53 genes. With each mutation, progressive changes are seen in the colonic epithelium (the cells on the internal surface of the colon). Normal epithelium is shown in first panel. Mutation of APC typically occurs early and is sometimes inherited. Mutations in APC lead to dysplasia or formation of a polyp (panel 2). When one cell in this polyp develops a second mutation, in the K-ras gene, it grows at a faster rate resulting in a benign Class I adenoma (panel 3). Subsequent mutations in DCC and p53 genes lead to late adenoma (panels 4 and 5) and finally carcinoma (panel 6). Once cancer forms, it can eventually break through the colon's cellular surface (panel 7) and spread through blood to other sites in the body. *(Illustration by Argosy Publishing.)*

through a process called biotransformation (a series of reactions in which the chemical structure of a compound is altered). The purpose of these reactions is to make the carcinogen more water-soluble so that it can be removed from the body. But these reactions can also convert a less toxic carcinogen into a more toxic one. Certain viruses can also act as carcinogens by interacting with DNA.

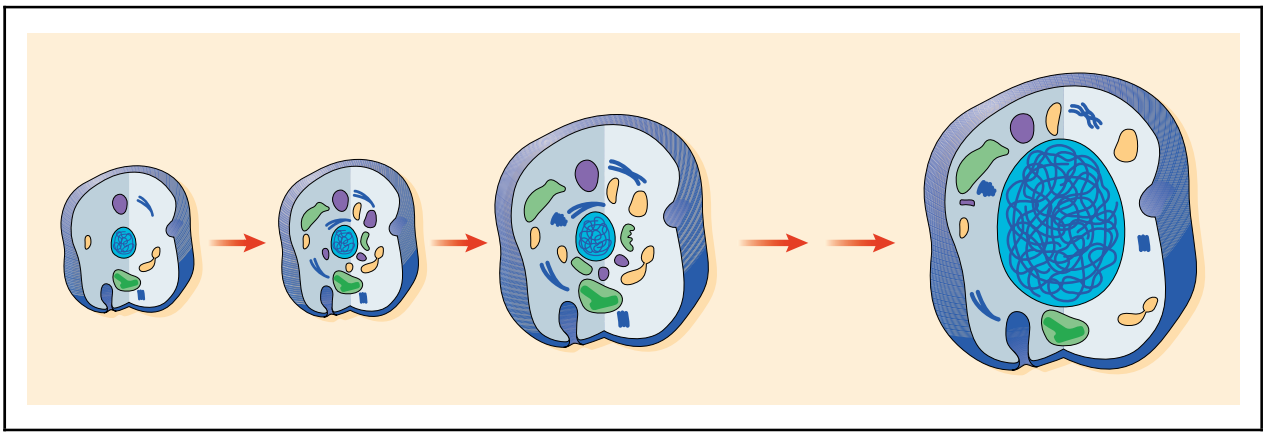
Nongenotoxins do not directly affect DNA but act in other ways to promote growth. These include hormones and some organic (carbon-based) compounds.

Stages of carcinogenesis

Cancer develops through four definable stages: initiation, promotion, progression and malignant conversion. These stages may progress over many years. The first stage, initiation, involves a change in the genetic makeup of a cell. This may occur randomly or when a carcinogen interacts with DNA causing damage. This initial damage rarely results in cancer because the cell has in place many mechanisms to repair damaged DNA. However, if repair does not occur and the damage to DNA is in the location of a gene that regulates cell growth and proliferation, DNA repair, or a function of the immune system, then the cell is more prone to becoming cancerous.

During promotion, the mutated cell is stimulated to grow and divide faster and becomes a population of cells. Eventually a benign tumor becomes evident. In human cancers, hormones, cigarette smoke, or bile acids are substances that are involved in promotion. This stage is usually reversible as evidenced by the fact that lung damage can often be reversed after smoking stops.

The progression phase is less well understood. During progression, there is further growth and expansion of the



Carcinogenesis. After several mutations, a normal cell becomes cancerous. The first stage of carcinogenesis, called initiation, involves a change in the genetic makeup of a cell. This may occur randomly or when a carcinogen interacts with DNA causing damage. This initial damage rarely results in cancer because the cell has in place many mechanisms to repair damaged DNA. However, if repair does not occur and the damage to DNA is in the location of a gene that regulates cell growth and proliferation, DNA repair, or a function of the immune system, then the cell is more prone to becoming cancerous. *(Illustration by Argosy Publishing.)*

tumor cells over normal cells. The genetic material of the tumor is more fragile and prone to additional mutations. These mutations occur in genes that regulate growth and cell function such as oncogenes, tumor suppressor genes, and DNA mismatch-repair genes. These changes contribute to tumor growth until conversion occurs, when the growing tumor becomes malignant and possibly metastatic. Many of these genetic changes have been identified in the development of **colon cancer** and thus it has become a model for studying multi-stage carcinogenesis.

Cancer genes

Oncogenes

Normal cell proliferation is controlled by growth factors and cytokines (mediating proteins) that act on the cell membrane, triggering a cascade of biochemical signals (a process called signal transduction). These signals control, among others, the genes that regulate cell growth and division. Oncogenes are altered forms of normal cellular genes called proto-oncogenes that are involved in this cascade of events. They may mutate spontaneously, through interaction with viruses, or by chemical or physical means.

When a proto-oncogene is altered to become an oncogene, the pathway of cell growth and proliferation become altered. This may lead to the abnormal growth of cells (neoplastic transformation). More than 100 oncogenes have been identified. An example of an oncogene is the K-ras gene that is mutated in colon cancer cells.

Genes are the means by which a cell produces proteins, each of which have a very specific role. A mutated gene can cause overproduction of a protein, underproduction of a protein, or alteration of a protein that may be unable to carry out its purpose. Oncogenes typically produce more of their protein product when mutated, while tumor suppressor genes typically produce less of their protein product when mutated.

Tumor suppressor genes

Both the activation of oncogenes and the inactivation of tumor suppressor genes appear to be necessary for cancer to occur. Tumor suppressor genes are typically associated with cell growth and differentiation and cell suicide (apoptosis). More than a dozen tumor suppressor genes have been identified. Proteins produced by tumor suppressor genes typically inhibit a cell from reproducing during times when growth is inappropriate such as during DNA repair; they are considered the "brakes" of the cell.

Mutations that inactivate the tumor suppressor gene p53 are the most common mutations seen in human cancers, accounting for about 50%. Carcinomas of the breast, colon, stomach, bladder and testis; **melanoma**; and soft tissue sarcoma all are linked to p53 mutations. The p53 protein is found in the nucleus of the cell and regulates cell functions such as cell growth, DNA repair, and apoptosis. The most notable role for p53 is to halt cell growth to allow the cell time to repair damaged DNA. If p53 is mutated, it loses this function, apoptosis does not occur, and unregulated cell growth results. In **Li-Fraumeni syndrome** a mutation of the p53 gene is inherited. This puts the individual at a high risk for a number of cancers such as early onset breast carcinoma, childhood **sarcomas**, and other tumors. Other tumor suppressor genes include the **retinoblastoma** gene and the DCC gene that is mutated in colon cancer.

KEY TERMS

Apoptosis—A process of cell death performed by a damaged cell.

Differentiation—A change to a more mature phenotype or appearance.

Dysplasia—A abnormal appearance of cells caused by cancer.

Malignant—A cancerous or invasive tumor.

Metastatic—A tumor with the ability to break off and grow in a distant location.

Mutation—A change in the genetic code that can be inherited or acquired.

Oncogene—A gene involved in normal cell growth that when mutated can lead to unregulated cell growth or cancer.

Proliferation—Reproduction of a cell. It differs from growth in that it is a change in number rather than size.

Tumor suppressor gene—A gene involved in slowing down cell growth so that if inactivated allows growth to progress without control.

DNA mismatch-repair genes

This more recently discovered class of cancer susceptibility genes is associated with the genetic instability of cancer cells that allows for multiple mutations to occur. This instability hastens the course of cancer. The normal function of these genes is to repair damage to the DNA. Mutations in DNA mismatch-repair genes are most notable in hereditary non-polyposis colorectal cancer (HNPCC).

Apoptosis

Apoptosis, also called cell suicide, refers to the death of a damaged cell. It is not random but occurs in cells with damaged DNA. When a cell becomes mutated and does not repair itself, it can be sacrificed to prevent that mutation from being passed on to the next generation of cells. Inhibition of apoptosis can be an essential step in carcinogenesis. Two genes involved in apoptosis are the tumor suppressor gene p53 and the bcl-2 proto-oncogene.

Colon carcinogenesis

Colon cancer has become a model for studying multi-stage carcinogenesis. Four distinct sequential mutations have been described in the development of colon cancer. These are mutations of the APC (adenomatous polyposis coli), K-ras, DCC (deleted in colon cancer), and p53 genes. With each mutation, progressive changes are seen in the colonic epithelium (the cells on the internal surface of the colon).

Mutation of APC typically occurs early and is sometimes inherited. Mutations in APC lead to dysplasia (abnormalities in adult cells) or polyp formation (usually benign growths on the surface of mucous membranes). These polyps can remain dormant for many decades. When one cell in this polyp develops a second mutation, in the K-ras gene, it grows at a faster rate resulting in a larger tumor or intermediate **adenoma**. Subsequent mutations in DCC and p53 lead to late adenoma and finally carcinoma.

These mutations result in both the overexpression of oncogenes and the deletion of anti-oncogenes, the combination of which results in cancer. This is, however, just a model and not all genes are altered in all cases of colon cancer; additional mutations are likely. Individuals with the hereditary predisposition to colon cancer known as familial adenomatous polyposis (FAP) typically have inherited mutations of the APC gene, the first step of colon cancer. Only 15% of colon cancer cases are due to hereditary factors, however, with 85% due to sporadic mutations.

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Cindy L. A. Jones, Ph.D.

Carcinoid tumors, gastrointestinal

Definition

Gastrointestinal carcinoid tumors are rare malignancies in which cancer develops in hormone-producing cells that line the appendix, bronchus, esophagus, intestines, liver, ovary, pancreas, rectum, stomach, testes, and thymus.

Description

Gastrointestinal carcinoid tumors are also called:

- carcinoids
- endocrine tumors, carcinoid type
- metastatic carcinoid tumors
- neuroendocrine tumors
- neuroendocrine cancers

Types of gastrointestinal carcinoids

Doctors describe gastrointestinal carcinoids according to the part of the gastrointestinal tract in which they originate. Foregut tumors start in the cells of the esophagus, bronchus, thymus, and stomach.

Midgut tumors originate in the: appendix, liver, ovary, small intestine, and parts of the large intestine.

Hindgut tumors originate in the rest of the colon or in the rectum.

About 75% of all carcinoid tumors originate in the digestive system. Most of them develop in the:

- small intestine (ileum)
- appendix
- rectum

Atypical tumor behavior

Most cancers cause symptoms in the organs in which they start or to which they spread (metastasize), but carcinoids can release chemicals (hormones) that travel through the bloodstream and cause symptoms in many parts of the body. These substances can damage heart valves, causing weakness, heart murmur, and shortness of breath.

Some gastrointestinal carcinoids stimulate the adrenal glands to produce abnormally high levels of the hormones that regulate the balance of water and salt in the body. Overproduction of these hormones causes weakness, weight gain, secondary diabetes, and excessive facial and body hair.

Carcinoid syndrome

Although gastrointestinal carcinoids behave differently in different people, tumors that originate in the appendix don't usually spread to other organs. Tumors that develop in the colon or rectum hardly ever produce hormones. Tumors that originate in the small intestine or other parts of the gastrointestinal tract and spread to the liver generally cause carcinoid syndrome. Flushing of the face and neck is the most common symptom of this rare malignant disease that affects the small intestine, stomach, and pancreas, and fewer than 10% of patients with gastrointestinal carcinoids.

Carcinoid syndrome is also characterized by:

- abdominal cramps
- breathlessness
- cyanosis
- **diarrhea**
- rapid heart beat (tachycardia)
- swelling around the eyes
- tearing
- wheezingStress, strenuous exercise, eating spicy foods, or drinking alcohol can intensify these symptoms.

Disease progression

Gastrointestinal carcinoids originate as small growths called tumorlets. These miniature tumors grow very slowly and few of them develop into carcinoid tumors.

The hormones that gastrointestinal carcinoids release generally cause more problems than the tumors themselves. Death usually results from heart or liver failure or from complications associated with tumor growth.

Demographics

About 2,500 carcinoids are diagnosed in the United States every year. African Americans develop carcinoids more often than Caucasians, and African-American women develop them more often than African-American men. Caucasian men and women are equally likely to develop these tumors.

The average age of patients diagnosed with carcinoid tumor of the appendix is 40. The average age of patients diagosed with carcinoid tumor of the stomach, small intestine, colon, and rectum is 55–65.

Causes and symptoms

The cause of gastrointestinal carcinoids is unknown, some risk factors have been identified. The risk factors that increase a person's risk of developing gastrointestinal carcinoids include:

- Having certain diseases that damage the stomach and decrease production of stomach acid. (Some of these diseases include chronic atrophic gastritis associated with pernicious anemia, chronic gastric infection with the *H. pylori* bacteria, auto-immune gastritis, or AIDS.)

- Having a family history of multiple endocrine neoplasia, type 1. (The multiple endocrine neoplasia (MEN) syndromes are three related disorders in which two or more of the hormone-secreting (endocrine) glands of the body develop tumors. Commonly affected glands are the thyroid, parathyroids, pituitary, adrenals, and pancreas. Patients diagnosed with this syndrome are at a higher risk for developing a variety of cancers, and require more frequent monitoring than the average patient might.)

Symptoms

Early-stage gastrointestinal carcinoids rarely cause symptoms. About half of these tumors are discovered during tests or surgical procedures performed to diagnose or treat other diseases of the digestive system.

The most common early symptom of gastrointestinal carcinoids is uncomfortable flushing of the face and neck. Most people who have gastrointestinal carcinoids eventually experience:

- abdominal cramps
- changes in bowel habits
- other symptoms similar to those of other intestinal cancers

Some gastrointestinal carcinoids cause:

- intestinal bleeding
- asthmatic wheezing
- impotence
- loss of interest in sex (libido)

Most patients develop abnormal connective tissue on the right side of the heart (endocardial fibrosis).

Diagnosis

If a patient has any abnormality that could be a symptom of a gastrointestinal carcinoid, the doctor asks about other symptoms that could be associated with carcinoid syndrome or caused by a tumor in the stomach, intestines, or rectum.

Diagnostic techniques

Doctors use a variety of diagnostic techniques to locate gastrointestinal carcinoids and determine how far the disease has spread:

- barium enemas and x rays highlight abnormalities in the lining of the esophagus, stomach, and intestines
- blood and urine tests measure amounts of substances that carcinoids secrete
- **colonoscopy** provides a view of the entire length of the colon
- endoscopic ultrasound shows how deeply tumors have penetrated the wall of the esophagus, stomach, intestines, or rectum and whether they have spread to nearby tissues
- octreoscan detects the spread of gastrointestinal carcinoids by using a special camera to track the path of injected radioactive hormone-like substances that are attracted to these tumors

Provocative testing designed to cause the patient to flush can help doctors diagnose some gastrointestinal carcinoids, can provoke potentially serious reactions, and must be performed in a hospital, under close medical supervision.

Biopsy

Diagnostic tests can indicate that a patient has a gastrointestinal carcinoid, but only **biopsy** can confirm the diagnosis. Endoscopic biopsy is the most common way to remove a sample of a suspected gastrointestinal carcinoid.

A doctor performs this procedure by passing a flexible lighted tube topped with a tiny video camera (endoscope) down the patient's throat or up through the anus to examine the lining of the organs of the digestive tract. After locating a tumor, the doctor manipulates pincers or tongs (biopsy forceps) through the endoscope to remove a tissue sample.

Clinical staging, treatments, and prognosis

Staging

Doctors divide gastrointestinal carcinoids into three categories.

- Localized cancer is found in the appendix, colon, rectum, small intestine, and stomach, but has not spread beyond the wall of the organ in which it originated.
- Regional spread describes tumors that have penetrated the wall of the organ in which they originated and have involved nearby fat cells, ligaments, muscles, and lymph nodes.
- Distant spread, or metastatic disease, refers to gastrointestinal carcinoids that have spread to the liver, bones, lungs, or other tissues or organs far from the original tumor.

Recurrent gastrointestinal carcinoid is disease that has returned after having been treated. Recurrent disease can develop at the site of the original tumor or in another part of the body.

Treatment

Treatment of gastrointestinal carcinoids is based on:

- where the tumor originated
- whether the cancer has spread beyond the gastrointestinal system
- the patient's general health

Surgery

Surgery cures most gastrointestinal carcinoids. What type of operation a patient undergoes depends on the size and location of the tumor, whether the patient has serious disease of any other organ, and whether the tumor is causing carcinoid syndrome.

TREATING LOCALIZED GASTROINTESTINAL CARCINOIDS A surgeon can usually remove all of a tumor that has not spread (is localized). This procedure, called local excision, consists of removing the tumor and nearby normal tissue, and sewing together the affected ends of the remaining tissue.

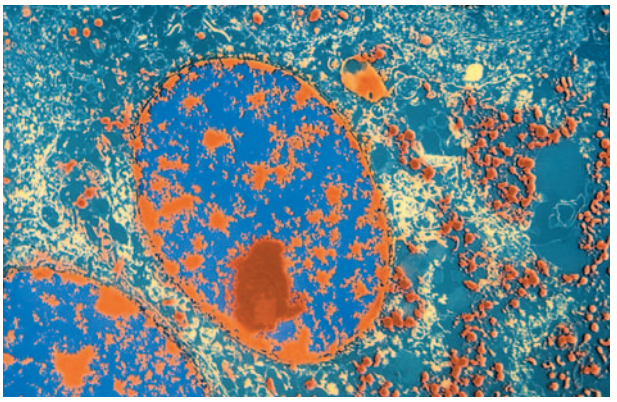
If a carcinoid originates in the appendix, doctors usually remove the appendix (appendectomy). If the tumor is larger than 3/4" (cm) and the patient is under the age of 60 and otherwise in good health, the doctor may also remove the third of the colon closest to the appendix, and nearby blood vessels and lymph nodes.

When a carcinoid tumor originates in the small intestine, doctors usually remove part of the bowel, and may remove nearby lymph nodes to see if they contain cancer cells. Local excision is used to remove carcinoids that are not much larger than 3/8" (cm). Surgery for larger tumors removes a greater amount of normal surrounding tissue and some nearby blood vessels and lymph nodes.

Doctors usually treat localized carcinoids that originate in the stomach, pancreas, and colon by removing the affected organ.

Local excision is used to treat carcinoids that are limited to areas of the large intestine other than the appendix or to the rectum. Doctors use a flexible lighted instrument (colonoscope) to remove small tumors from these sites and remove larger tumors through an incision in the patient's abdomen.

Electrofulguration, a surgical procedure sometimes used to cure rectal carcinoids, destroys the tumor by heating it with electrical current. Doctors use electrofulguration to burn away rectal carcinoids no larger than 3/8". Tumors measuring 3/4" or more are apt to grow and metastasize and must be surgically removed.



Colored transmission electron micrograph of a cancer cell from a carcinoid tumor of the human gut. The large oval is the cell nucleus. The red patch inside it is the nucleolus, often prominent in cancer cells. The small red granules in the cytoplasm are packed with the hormone serotonin. High levels of this hormone can cause symptoms like wheezing and diarrhea. *(Copyright Science Photo Library/Photo Researchers, Inc. Photo reproduced by permission.)*

Segmental colon resection (also called hemicolectomy) removes between one-third and one-half of the large intestine, and blood vessels and lymph nodes near the affected tissue.

Abdominoperineal resection is used for very large or very invasive carcinoids of the lower rectum. A patient who has this operation also has a **colostomy**. Deeply invasive rectal carcinoids that measure less than 3/4" are treated like larger tumors. Mildly invasive tumors of comparable size are treated with local excision and careful monitoring to check for recurrence.

Lower anterior resection is used for some carcinoids in the upper part of the rectum. This procedure removes some of the rectum before the remaining ends are sewn together, and has little lasting effect on the digestive system.

TREATING REGIONAL SPREAD When a gastrointestinal carcinoid has spread to organs or tissues close to the original tumor (regional spread), doctors usually remove the affected organ. Some nearby organs and tissues may also be removed.

If it is not possible to completely remove a gastrointestinal carcinoid that has spread to another part of the body, surgeons remove as much of the cancer as they can without damaging vital organs or causing severe side effects. Surgery cannot cure gastrointestinal carcinoids that have spread to parts of the body far from the original tumor, but it can relieve symptoms and slow the progression of the disease.

Liver resection removes one or more metastases (secondary tumors) from the liver. This procedure does

KEY TERMS

Adrenal gland—Either of two glands that secrete hormones that maintain the balance of water and salt in the body and regulate the functions of other organs. Also called suprarenal glands.

Cyanosis—Bluish discoloration of the skin.

Heart murmur—Abnormal heart sound heard through a stethoscope.

Hormone—Chemical that is produced in certain cells of the body and that controls the activity of other cells.

Secondary diabetes—Form of diabetes resulting from damage to the pancreas.

not cure cancer but can relieve symptoms of carcinoid syndrome. Doctors destroy gastrointestinal carcinoids that have spread to the liver by:

- using images generated by a CT scan (**computed tomography** scan) to guide a long thin needle into tumors and injecting them with concentrated alcohol
- cooling the needle with liquid nitrogen to freeze carcinoid tumor cells (cryosurgery)

TREATING METASTATIC DISEASE Doctors treat gastrointestinal carcinoids that have spread to distant parts of the body by:

- freezing and killing cancer cells
- performing surgery or administering radiation or **chemotherapy** to relieve symptoms
- using biological therapy to stimulate the patient's immune system to attack tumor cells

Neither radiation nor chemotherapy can cure gastrointestinal carcinoids. Doctors sometimes use external beam radiation to treat patients who are too ill or frail to withstand surgery, and to relieve pain caused by tumors that have spread to the bones.

Doctors may use several different chemotherapy drugs or combine a chemotherapy drug with other medication to slow tumor growth and relieve symptoms. Chemotherapy is generally used only for gastrointestinal carcinoids that have spread to other organs, cause severe symptoms, and have not responded to other treatments.

Doctors sometimes treat gastrointestinal carcinoids that have spread to the liver by injecting chemotherapy drugs directly into the artery that supplies blood to the liver (hepatic artery). This technique (intra-arterial chemotherapy):

- exposes liver tumors to high doses of cancer-killing drugs
- prevents side effects by shielding healthy tissues from these powerful medicationsWhen doctors also inject material that blocks the hepatic artery, this treatment is called **chemoembolization**.

Octreotide is a hormone-like drug that can prevent or relieve flushing, wheezing, diarrhea, and other symptoms that sometimes occur during surgery or when gastrointestinal carcinoids release high levels of hormones. Octreotide can temporarily shrink these tumors but does not cure the cancer. Some patients experience pain at the site where the medication is injected, cramps, **nausea and vomiting**, dizziness, and **fatigue**.

Doctors also prescribe other medications to relieve specific symptoms.

Biological therapy, or Interferon-alpha therapy may stimulate the patient's immune system to attack the tumor, shrink metastatic gastrointestinal carcinoids, and may relieve symptoms of carcinoid syndrome. This technique, which is also called immunotherapy, is sometimes used to treat tumors that have not responded to chemotherapy or octreotide, but can cause severe flu-like side effects.

TREATING RECURRENT DISEASE Treatment of recurrent disease depends on where the new tumor is located and what treatment the patient has already received.

TREATING CARCINOID SYNDROME Treatments for carcinoid syndrome include surgically removing the cancer, blocking the hepatic artery or injecting chemotherapy drugs into it, medication to relieve symptoms, and stimulating the patient's immune system to attack the tumor.

LONG-TERM SURVEILLANCE After completing treatment, patients with certain types of gastrointestinal carcinoids must continue to have regular physical examinations, x rays, and blood and urine tests to help doctors detect recurrence during the earliest stages of disease.

Because some gastrointestinal carcinoids recur many years after initial treatment, high-risk patients should continue to see their doctor regularly. Any patient who has had a gastrointestinal carcinoid should immediately notify the doctor of any new symptoms. These symptoms could be side effects of treatment or a sign that the cancer has returned.

Prognosis

The only way to cure gastrointestinal carcinoids is to remove the tumors surgically. But because these cancers

grow so slowly, it is not unusual for a patient to survive 10–15 years after being diagnosed with metastatic disease.

5-YEAR SURVIVAL RATES For patients whose carcinoid tumor originates in the stomach, the 5-year survival rate is:

- 64% for localized disease
- 40% for regional spread
- 10% for mestatatic disease

When tumors originate in the small intestine, the 5-year survival rate is:

- 65% for localized disease
- 66% for regional spread
- 36% for metastatic disease

For carcinoids that originate in parts of the colon other than the appendix, the 5-year survival rate is:

- 71% for localized disease
- 44% for regional spread
- 21% for metastatic disease

For carcinoids that originate in the appendix, the 5-year survival rate is:

- 94% for localized disease
- 85% for regional spread
- 34% for metastatic disease

For carcinoids that originate in the rectum, the 5-year survival rate is:

- 81% for localized disease
- 47% for regional spread
- 18% for metastatic disease

Having a gastrointestinal carcinoid increases a patient's risk of developing other cancers in the digestive system.

Clinical trials

Researchers are investigating:

- how changes in cells transform normal tissues into gastrointestinal carcinoid tumors
- how effectively specific chemotherapy drugs and surgical procedures treat gastrointestinal carcinoids
- new ways of slowing or preventing growth of gastrointestinal carcinoids by blocking or shrinking the blood vessels that nourish them
- how nuclear medicine can contribute to early detection of gastrointestinal carcinoids

QUESTIONS TO ASK THE DOCTOR

- What kind of gastrointestinal carcinoid do I have?
- What kind of treatment should I have?
- Will this treatment cure my disease?
- What are the side effects of this treatment?

Prevention

There is no known way to prevent gastrointestinal carcinoids or to reduce the risk of developing them, but avoiding the following can prevent symptoms of carcinoid syndrome from becoming more intense:

- alcoholic drinks
- hot, spicy foods
- strenuous exercise
- stress

See also Cryotherapy; Gastrointestinal cancers; Hepatic arterial infusion; Neuroendocrine tumors.

Resources

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Maureen Haggerty

Carcinoid tumors, lung

Definition

Lung carcinoid tumors are rare malignant growths that develop from cells that help regulate the flow of air and blood through the lungs. These growths are also known as neuroendocrine lung tumors, pulmonary carcinoids, and lung carcinoids.

Description

These cancers account for 1% to 3% of all lung tumors. Most lung carcinoids measure between slightly less than 1/4" (0.63 cm) and slightly more than 3/4" (1.9 cm). These tumors usually develop in the right lung.

Doctors classify lung carcinoids according to what tumor cells look like under a microscope, and where in the lung the tumor is located. Typical lung carcinoids occur about nine times as often as atypical tumors. They grow slowly and rarely spread beyond the lungs. Atypical lung carcinoids grow somewhat faster than typical tumors and are more likely to spread to other organs. In their most invasive form, atypical lung carcinoids look and behave like small-cell lung cancers.

About 80% of lung carcinoids are central carcinoids. Located in the walls of the large airways in the center of the lungs, where the neuroendocrine cells that form them are most concentrated, these tumors are almost always typical tumors. Carcinoids that develop in the narrower airways, close to the edges of the lungs, are called peripheral carcinoids. Most are typical tumors.

Demographics

Lung carcinoids usually develop between the ages of 45 and 55. These tumors are equally common in men and women and rarely affect children.

Causes and symptoms

Lung carcinoids are not caused by smoking or by exposure to chemicals at work or in the environment. Doctors believe that central carcinoids develop from glands beneath the surface of the large air passages. Lung biopsies performed to diagnose or treat other conditions sometimes reveal microscopic clusters of neuroendocrine cells. These carcinoid tumorlets look like tiny peripheral carcinoids. They are most common when disease has caused scar tissue to form in the lungs, and may grow to be carcinoid tumors.

Patients who have peripheral or small central carcinoids don't usually show symptoms, but some patients who have central carcinoids cough, wheeze, or cough up blood (**hemoptysis**).

A large carcinoid that blocks part or all of an airway can cause post-obstructive **pneumonia**. Doctors may not consider the possibility of a carcinoid until **antibiotics** fail to cure this lung infection.

About 10% to 20% of lung carcinoids produce hormone-like substances that release into the bloodstream. These substances can cause symptoms such as **Cushing's syndrome**, acromegaly, or **hypercalcemia**. They may also cause carcinoid syndrome, which is a constellation of symptoms including facial flushing, abdominal cramps, **diarrhea**, and breathlessness, among others.

Diagnosis

A thorough physical examination will detect symptoms of syndrome health problems associated with these tumors. If a patient has one or more symptoms that suggest the presence of a lung carcinoid, the doctor will inquire about:

- chest pain
- cough
- blood-tinged sputum
- asthma
- wheezing
- pneumonia not cured by antibiotics
- recent weight gain
- facial flushing
- diarrhea The doctor will use one or more methods to determine whether the patient has a lung tumor. Lung carcinoids that do not cause symptoms usually show up on chest x rays taken during a routine physical or as a result of other health problems.

Chest x rays cannot detect tumors that are very small or hidden by other organs in the chest. A doctor

who suspects a lung carcinoid may order additional **imaging studies** in order to make a more detailed search.

About 75% of lung carcinoids can be seen through a long, lighted tube called a bronchoscope. Doctors also use CT scans, octreoscans, or MIBG (metaiodobenzylguanidine) scans to locate lung carcinoids and determine how far they have spread. CT scans provide a detailed view of the lungs. Octreoscans and MIBG scans trace the path of radioactive substances that are attracted to lung carcinoids.

Also called indium-111-labeled DTPA-octreotide scintigraphy, octreoscan involves injecting a small amount of a radioactive hormone-like substance into the patient's vein. Carcinoid tumors attract this substance, and a special camera locates tumors by pinpointing the area where the radioactive material accumulates.

Doctors perform MIBG scans by attaching radioactive iodine to a chemical absorbed by carcinoid tumors. This compound is injected into the patient's bloodstream, drawn to carcinoid tumor cells, and tracked by a special scanner.

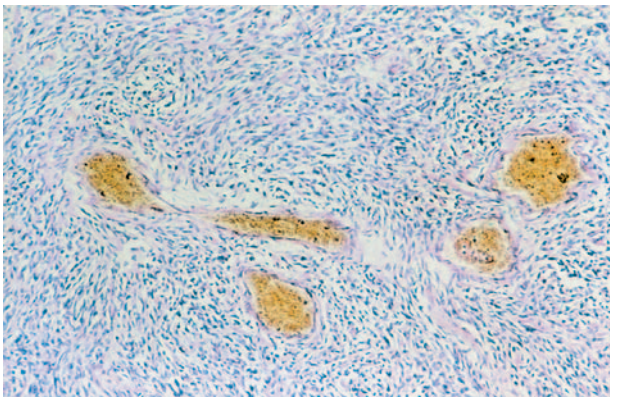
Although diagnostic procedures can indicate that a patient might have a lung carcinoid, **biopsy** is the only way to confirm the diagnosis. Doctors use several different techniques to remove samples of these tumors.

BRONCHOSCOPIC BIOPSY To obtain a sample of a tumor in one of the large airways, the doctor uses a bronchoscope to examine the lining of these organs. When a tumor is located, the doctor manipulates pincers or tongs (biopsy forceps) through the bronchoscope to remove a small sample of tissue. The patient leaves the hospital a few hours after undergoing this outpatient procedure. If serious bleeding occurs, the doctor narrows or seals the blood vessels by injecting drugs or aiming a laser beam.

BRUSHING SAMPLE A doctor who performs a bronchoscopic biopsy may also wipe a tiny brush over the surface of the tumor. Tumor cells extracted in this way (brushing sample) are examined under a microscope. A brushing sample can add useful information to the results of bronchoscopic biopsy.

NEEDLE BIOPSY Doctors often use needle biopsy to obtain samples of tumors that are not close to the large airways. Guided by a **computed tomography** scan (CT scan) image, a long needle is passed between the ribs and into the lung to remove a small piece of the tumor. Because carcinoid tumors are usually small, localization using a needle biopsy may be difficult or impossible.

THORACOTOMY If neither bronchoscopic biopsy nor needle biopsy yields enough tissue to identify the tumor type, the doctor may open the patient's chest (**thoracotomy**) to remove a tissue sample. A doctor who feels certain that a tumor is a carcinoid may perform a thoracotomy and remove the entire tumor without having taken a biopsy sample.



Lung carcinoid, spindle cell form. *(Copyright Parviz M. Pour, Science Source/Photo Researchers, Inc. Photo reproduced by permission.)*

Treatment team

Lung carcinoids are treated by thoracic and cardiothoracic surgeons.

Clinical staging, treatments, and prognosis

Staging

Once lung carcinoids have been diagnosed, more tests are done to find out if the cancer has spread from the lung to other parts of the body (staging). A doctor needs to know the stage to plan treatment. Doctors stage lung carcinoids the same way they stage non-small cell lung cancers:

- Stage 0: Cancer is only found in a local area and only in a few layers of cells. It has not grown through the top lining of the lung.
- Stage I: The cancer is only in the lung, and normal tissue is around it.
- Stage II: Cancer has spread to nearby lymph nodes.
- Stage III: Cancer has spread to the chest wall or diaphragm near the lung; or the cancer has spread to the lymph nodes in the area that separates the two lungs (mediastinum); or to the lymph nodes on the other side of the chest or in the neck. Stage III is further divided into stage IIIA (usually can be operated on) and stage IIIB (usually cannot be operated on).
- Stage IV: Cancer has spread to other parts of the body.

KEY TERMS

Acromegaly—Hormonal disorder causing progressive enlargement of hands and feet and elongation of the face, headache, muscle pain, and visual and emotional disturbances in middle-aged men and women.

Carcinoid syndrome—Rare malignant disease characterized by facial flushing, abdominal cramps, diarrhea, breathlessness, and other symptoms. Affects fewer than 10% of patients with carcinoid tumor.

Cushing's syndrome—Hormonal disorder characterized by a round face, mental or emotional instability, high blood pressure, weight gain, or abnormal growth of facial and body hair in women.

Emphysema—Abnormal lung condition characterized by breathing problems, cough, rapid heartbeat. Later stages are characterized by restlessness, weakness, confusion, increased breathlessness, and may cause fluid to collect around the lungs (pulmonary edema) and congestive heart failure.

Hypercalcemia—Abnormally high levels of calcium in the blood, causing muscle pain and weakness and loss of appetite. Severe cases can result in kidney failure.

Treatment of lung carcinoids

Doctors consider tumor size and location, and whether the patient has additional lung problems or serious disease affecting any other organ, in order to determine the most appropriate treatment for lung carcinoids.

SURGERY Removing the tumor (surgical resection) is the treatment of choice for these cancers because most lung carcinoids:

- can be cured by surgery alone
- do not respond to **chemotherapy** or radiation
- must be removed in order to prevent airway obstruction and other complications of tumor growth

If the tumor is located in a large airway, the surgeon may remove the tumor and normal tissue above and below it, then sew together the remaining lung tissue. This procedure is a sleeve resection.

If tumor size or location makes sleeve resection impossible, the surgeon removes the affected lobe of the lung (**lobectomy**). In rare cases, the surgeon removes the entire right or left lung (**pneumonectomy**).

Surgeons use lobectomy to remove peripheral carcinoids located at the edges of the lungs farthest from the large airways. If the tumor is very small, the surgeon may remove it and a wedge-shaped piece of lung tissue surrounding it (wedge resection).

Surgeons who remove lung carcinoids usually remove some of the lymph nodes near the lungs because:

- About 10% of typical carcinoids and 30% to 50% of atypical carcinoids have spread to lymph nodes by the time the disease is diagnosed.
- Not removing lymph nodes might increase the risk of cancer spreading to other organs.
- Surgery alone cannot cure lung carcinoids that have spread to other organs.
- Examining lymph nodes can indicate the likelihood that cancer will recur.Surgeons who remove lung carcinoids try to preserve the patient's lung function by removing the smallest possible amount of normal lung tissue.

PALLIATIVE TREATMENT A patient who has severe emphysema, chronic bronchitis, heart disease, or other medical problems may not be able to withstand the stress of surgery to cure lung carcinoids or to cope with breathing difficulties resulting from removal of normal lung tissue.

Doctors use a bronchoscope and a laser to burn away (vaporize) most of the tumor in a patient who is too ill to withstand surgery. These palliative treatments can relieve most symptoms associated with lung carcinoids, but cannot cure the disease. They are often supplemented by radiation administered externally or directly into the air passages (intrabronchial radiation).

MEDICAL TREATMENTS Guidelines issued in 2001 by the National Comprehensive Cancer Network recommend the use of radiation following surgery to remove carcinoid lung tumors, and chemotherapy and radiation following surgery to remove atypical lung carcinoids.

Injected into a vein or taken by mouth, chemotherapy drugs are also used to treat lung carcinoids that have spread to other organs, are causing severe symptoms, or have not responded to other medications. Doctors may combine two or more chemotherapy drugs or add them to other medications to relieve symptoms of lung carcinoids that have spread to other organs.

Octreotide controls wheezing, flushing, and other symptoms of carcinoid syndrome. This medication may temporarily shrink lung carcinoids but does not cure them.

Alpha-interferon can shrink some lung carcinoids that have spread to other parts of the body and relieve

symptoms of carcinoid syndrome. Doctors can prescribe other medications to relieve specific symptoms.

Radiation may be an option for patients who are too frail or ill to undergo surgery but is not a very effective treatment for lung carcinoids. High doses of radiation can damage lung tissue, create scar tissue, cause breathing problems, and make the patient more susceptible to infection.

PROGNOSIS Five-year survival rates for patients with lung carcinoids are 90% to 100% for typical tumors, and 40% to 76% for atypical tumors. Ten-year survival rates are about 10% lower than five-year rates for both types of tumors. The prognosis is worse for lung carcinoids that measure 1 1/4" (3.2 cm) or larger or have spread to lymph nodes.

Some patients who have had lung carcinoids must continue to have regular x rays and blood tests to help doctors detect recurrent disease in its earliest stages. Any patient who has had a lung carcinoid should notify the doctor whenever new symptoms develop. These symptoms could be side effects of treatment or signs that the disease has recurred. A patient who has recovered from surgery should ask the doctor about an exercise routine to restore energy and reduce shortness of breath.

Clinical trials

Researchers are currently investigating whether:

- new methods of delivering radiation can shrink lung carcinoids that have not responded to treatment
- inhaling chemotherapy drugs can shrink advanced lung carcinoids
- biological therapy can starve lung carcinoids by cutting off the flow of blood that nourishes them and stimulate patients' white blood cells to kill cancer cells
- new methods of delivering chemotherapy can kill cancer cells without harming normal cells
- new combinations of chemotherapy drugs can prevent cancer cells from multiplying
- chemotherapy drugs combined with radioactive substances can locate and kill cancer cells without harming normal cellsInformation about **clinical trials** is available from the National Institute of Health's National Cancer Institute.

Prevention

There are no known risk factors for lung carcinoids, and no methods of prevention are known.

See also Bronchoscopy; Neuroendocrine carcinomas.

QUESTIONS TO ASK THE DOCTOR

- What kind of lung carcinoid do I have?
- What treatment do you recommend?
- Will this treatment cure me?
- What can I do to make this treatment more successful?

Resources

PERIODICALS

"New NCCN Recommendations for Small-Cell Lung Cancer." *Oncology News International* 10, no. 4 (April 2001).

ORGANIZATIONS

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National Cancer Institute. *CancerNet*. [cited May 28, 2001]. <http://cancernet.nci.nih.gov>.

Maureen Haggerty

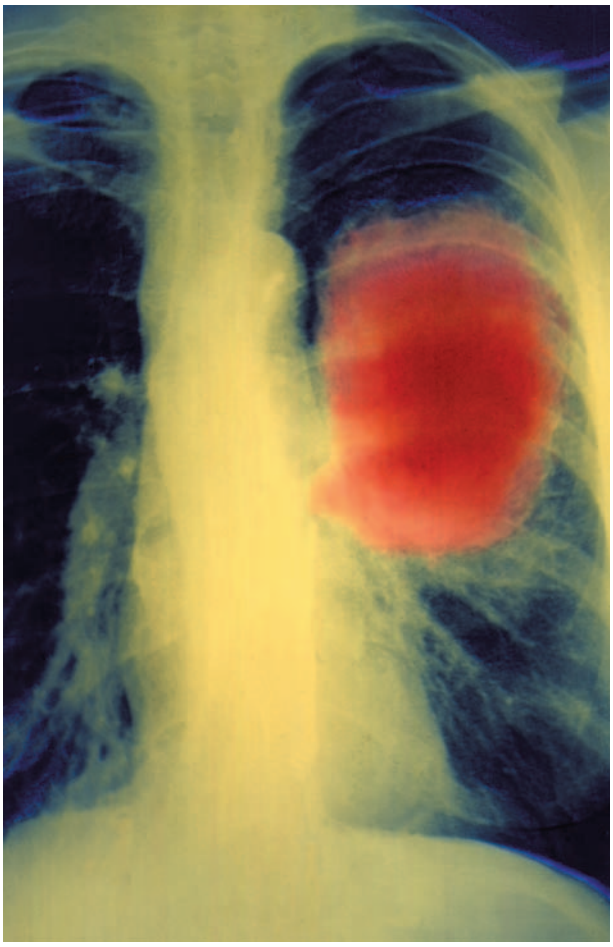
Carcinoma

Definition

A malignant tumor that arises from epithelial cells, which line the internal and external surfaces of the body. Carcinomas are most commonly found in the lining of body organs, such as the breast, prostate, lung, stomach, or bowel. Most human cancers are carcinomas.

See also Carcinoma of Unknown Primary.

Kate Kretschmann



X ray showing presence of carcinoma. *(Photo Researchers, Inc. Reproduced by permission.)*

Carcinoma of unknown primary

Definition

Carcinoma of unknown primary (CUP) is a disease in which malignant (cancerous) cells are found in the body, but the organ where they initially began growing, the **primary site**, cannot be discovered.

Description

The area where a cancer originates in the body is often referred to as the primary tumor. Cancer of unknown primary is a cancer that starts out in an unknown spot and then metastasizes (spreads) to another site, such as a lymph node, the liver, lung, brain, or the bones. Because the primary site is unknown, prognosis may differ from patient to patient.

Most cancers are named after the area of the body in which they start. For example, **breast cancer** is cancer that originates in the breast. If it spreads to another part of the body, it is still called breast cancer, and the cancerous cells that have metastasized still look like breast cancer cells. With CUP, however, doctors are unable to know with certainty the origin of these cells.

Demographics

According to the American Cancer Society, about 35,000 cases of cancer of unknown primary are diagnosed each year. These represent approximately 3% to 5% of all cases of cancer. The average age of a patient diagnosed with CUP is approximately 58. The disease is more common in men than in women.

Causes and symptoms

Every cancer has distinct risk factors, or causes. It is difficult to identify specific causes of CUP since the exact type of cancer is unknown.

The symptoms of carcinoma of unknown primary are organ-specific. These symptoms may include:

- Lymphadenopathy, a condition in which the lymph nodes are swollen, firm to the touch, but do not hurt. Cancers frequently spread to the lymph nodes.
- A mass in the abdomen or a feeling of abdominal fullness. This is often caused by a cancer growing in the liver or the spleen, or by a collection of fluid inside the abdomen called ascites.
- Shortness of breath. This symptom may be caused by cancer that has spread to the lungs or from **pleural effusion**, a build-up of fluid and cancer cells in the area around the lungs.
- Pain in the chest or abdomen. Cancer growth around nerves or tumors pressing against internal organs may cause these symptoms.
- Bone pain. Severe pain may occur when cancer has spread to the bones. Bones that are made weak by the cancer's spread may contribute to fractures. These fractures may result from minor injuries, or even from normal activities, like rolling over in bed.
- Skin tumors. Some cancers start out in organs and spread through the bloodstream to the skin. Skin metastases are sometimes the first sign of spread from a cancer of unknown primary.
- Weakness, **fatigue**, poor appetite, and **weight loss**. These generalized symptoms may happen because the cancer has spread to specific organs or systems. Also, some cancers release hormone-like substances into the bloodstream that affect metabolism and cause these same problems.

Diagnosis

The initial step in evaluating a person with cancer is a medical history and general physical exam. These simple steps may suggest the origin of the cancer. If this is not apparent, various imaging tests, blood tests, and endoscopic exams may be used. A **biopsy** would be performed for routine study under the microscope. The biopsy is the most important of these tests, as it is needed to confirm the diagnosis of cancer. Once the presence of cancer is confirmed, the doctor will then attempt to find its source. Selecting which tests to perform is dependent upon which cancers are likely to occur in a person of the patient's age and gender.

Many of the tests done on a patient with CUP are geared towards finding the primary site. Blood cell counts and blood cell examination will be performed, because changes in the numbers of different blood cell types may suggest that a cancer of unknown primary has spread to the bones. Another type of blood test commonly done at this diagnostic stage is the serum tumor marker, which measures the amount of substances that are secreted by some cancers into the bloodstream. If these substances are present in the blood of patients with CUP, they can provide clues to the origin of the cancer.

The next diagnostic step is usually a biopsy. The samples obtained for the biopsy will undergo various laboratory tests to help place the cancer into a category that will guide the doctor in choosing appropriate treatment. In addition to biopsies, various **imaging studies** may be performed to produce pictures of the inside of the body. X rays are often done to determine the presence of a mass, but they are not usually useful in finding out what type of cancer is present or in what organ it began. A **computed tomography** (CT) scan is often done to produce a detailed picture of the inside of the body, and can often depict the amount of cancer spread throughout the body. CT scans also aid in finding primary tumors in the throat, sinuses, pancreas, ovaries, and some other organs. **Magnetic resonance imaging** (MRI) takes pictures similar to, but more detailed than, the CT scan. Ultrasounds may show which organs have been affected by CUP, but only rarely can they help find the cancer's site of origin.

In order to receive a diagnosis of cancer of unknown primary, the patient must have had the following done in an attempt to find the origin:

- complete medical history and physical exam
- complete blood cell count and routine blood chemistry tests
- biopsy of the metastatic tumor with a microscopic examination of the cancer cells, along with certain other tests
- if the tumor is found in the abdomen or in the lymph nodes of the groin, a chest **x ray** and CT scan of the abdomen and pelvis
- ultrasound of the testicles (in males) or pelvis (in females)
- mammogram
- routine testing of the urine
- testing of the stool for blood, which may indicate cancer of the digestive system
- examination of the gastrointestinal (GI) tract
- thyroid scan

If all of these examinations are done, and the primary tumor site is still undetermined, then the patient is given the diagnosis of carcinoma of unknown primary. Based on the cancer's location and classification, doctors will determine which additional tests should be performed.

Treatment team

The patient's primary physician as well as an oncologist will be involved in the care of a patient with CUP. Nurses of various specialties, including those who provide **chemotherapy**, will be involved. Because of the unique nature of this disease, a pathologist plays a central role in making a diagnosis. There is probably no more important clue to diagnosing a CUP than a thorough evaluation of a specimen. These evaluations provide guidance for the decisions that follow by the oncologist and primary physician.

Clinical staging, treatments, and prognosis

Most types of cancer are placed in stages I, II, III, or IV. These stages are based on the extent of spread and whether or not the cancer has moved to lymph nodes or other organs. Each stage classification is slightly different for each type of cancer. Stage I is the least extensive, with the best prognosis (outlook), and Stage IV cancers have the worst prognosis with the most spread. It is impossible to stage cancers of unknown primary accurately because the type of cancer is unknown. However, in order for it to be considered a CUP, the cancer must have spread beyond the primary site. Therefore, all CUP's are considered a stage IV cancer.

Many different treatments are used either alone or in combination to treat cancer of unknown primary. Some of the treatments include surgery, **radiation therapy**, chemotherapy, and hormone therapy. Surgery is commonly used to treat CUP. A surgeon may remove the cancer as well as some of the healthy tissue around it. Radiation therapy uses x rays or other high-energy rays to kill cancer cells and shrink tumors. It may be used alone or before or after

KEY TERMS

Chemotherapy—The treatment of disease by means of chemicals that have a specific toxic effect on the disease-producing microorganisms or that selectively destroy cancerous tissue.

Metastasis—The process in which cancer cells travel or spread from their original site to other parts of the body.

Primary site—The area in the body where a cancer originates.

surgery. Radiation for CUP may be given in two ways—externally or internally. The most common radiation treatment for CUP is given from a machine outside the body. The patient is normally treated five days a week for several weeks. Chemotherapy uses drugs to kill cancer cells. It is a systemic treatment, since it travels throughout the body by the bloodstream. The most common drugs used to treat cancer of unknown primary are: **paclitaxel**, **etoposide**, **cisplatin** or **carboplatin**, **bleomycin**, **vinblastine**, 5-fluorouracil (also simply called **fluorouracil** or 5-FU), and **ifosfamide**.

Several factors are considered when determining which treatment to use for CUP. Although many cancers of unknown primary cannot be cured, treatment may help the patient to live longer or improve the quality of life. Patient and doctor should discuss potential benefits of treatment as well as possible side effects.

The general prognosis for patients with CUP is poor. As a group, the survival rate is around three to four months with less than a 25% survival rate one year after diagnosis, and a 10% survival rate after five years. Although the majority of cancers of unknown primary are resistant to treatment, there are certain types of CUP that have a much better outlook. These subgroups respond better to treatment and reemphasize the importance of the pathologist in evaluating the cancer cells. When cancer of unknown primary has spread to multiple internal organs, the five-year survival rate after diagnosis is at approximately 5%. There are several reasons for the serious prognosis of CUP. Most of these cancers spread rapidly. In addition, it is difficult to know what treatment will be the most effective since the exact type of cancer is not known. Finally, a cancer of unknown primary has already spread beyond its original site by the time the diagnosis is made.

Alternative and complementary therapies

Since most cases of CUP have a poor prognosis, even with the use of traditional treatment, many patients with CUP may be interested in seeking out alternative and complementary therapies. The most commonly sought out alternative therapies include dietary treatments, herbs, homeopathy, hypnotherapy, meditation, **vitamins**, relaxation and spiritual healing. Many complementary therapies like music and massage, meditation, and herbal teas to relieve nausea are well documented in their abilities to relieve stress and enhance feelings of well being. At the same time, however, it is important to realize that many proposed remedies have not been studied, and may even contain potentially harmful ingredients. Herbs have become very popular, but many have harmful interactions with other medicines. It is important for a patient interested in alternative treatments to discuss this decision with health care professionals.

Coping with cancer treatment

No one can predict how a patient will respond to treatment. Many factors impact how a patient will cope, including a strong family support system, a healthy immune system, or a deep religious faith. Cancer treatment can cause great fatigue. Patients should allow time to recover without feeling the need to resume normal activities immediately. Eating a healthy, balanced diet and slowly increasing activity will help a patient with CUP regain strength and energy.

Clinical trials

Research regarding the nature and treatment of cancer of unknown primary is being conducted in several areas. New chemotherapy drugs, drug combinations, methods of administering chemotherapy, and the effect of peripheral stem cell transplantation on CUP are currently under study. In addition, gene therapy is also being tested as a treatment for CUP. Other approaches under examination include sensitizing the body's immunologic T cells against cancer cells, as well as using **vaccines**. Since CUP is a term for several different types of cancer, an improved overall understanding of cancer can help the medical community create improved treatments. One of the ways this happens is through participation in **clinical trials**. The patient with cancer of unknown primary can find out what clinical trials are available by contacting the National Cancer Institute.

Prevention

Since the exact type of cancer involved in CUP is not known, it is difficult to say just how that cancer might have been prevented, if at all. The risk factors are difficult to identify. Autopsy studies, however, can be of assistance. Patients who have died of CUP show that many of the cancers began in the pancreas, lungs, kid-

QUESTIONS TO ASK THE DOCTOR

- What treatment choices do I have? Which do you recommend, and why?
- What side effects from treatment can I expect, and what can I do to help reduce them?
- What are the chances that my CUP will return once I am in remission?

neys, throat, larynx, or esophagus. Smoking is a significant risk factor for each of these cancers.

Other sites of CUP include the stomach, colon, or rectum. High-fat dietary habits are linked to these cancers. Fresh fruits, vegetables and high-fiber foods offer the greatest dietary protection. Another source of CUP is a type of skin cancer termed malignant **melanoma**. Its primary risk factor is unprotected exposure to the sun.

Special concerns

The inability to identify a primary site for metastatic cancer can generate a great deal of anxiety, anger and frustration for patients and family. They may believe that the physician is incompetent or that the prognosis would be improved if a primary site could be definitively identified. Though it is important to do necessary diagnostic testing, it is common for patients and families to encourage a physician to keep testing well beyond the point in which the primary tumor is likely to be discovered. At this stage, the presence of metastatic tumors indicates that the cancer has already spread, and it is important to start treatment as soon as possible.

Resources

PERIODICALS

Cassileth, Barrie R. "Evaluating Complementary and Alternative Therapies for Cancer Patients." *CA: A Cancer Journal for Clinicians* November-December 1999: 353-61.

Ward, Darrell. "The Case of the Missing Primary." *Frontiers* Spring-Summer 1999: available at <http://www.osu.edu/units/cancer/frontier.htm>.

ORGANIZATIONS

American Cancer Society. (800)ACS-2345. <http://www.cancer.org>.

National Cancer Institute. Building 31, Room 10A31, 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. <http://www.nci.nih.gov>.

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National Coalition for Cancer Survivorship. [cited June 8, 2001]. <http://www.cansearch.org>.

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Carcinomatous meningitis

Definition

Carcinomatous meningitis, also called meningeal carcinomatosis, neoplastic meningitis, or leptomeningeal carcinoma, is a form of metastatic cancer that has spread to the lining of the brain and spinal cord, the parts of the body that make up the central nervous system.

Description

The meninges are membranes that cover the brain and spinal cord. There are two types of meninges, thin membranes called the pia-arachnoid or leptomeninges, and firmer, tougher membranes called the dura or pachymeninges. Carcinomatous meningitis is cancer of the leptomeninges. These membranes are bathed in and help contain cerebrospinal fluid (CSF).

Carcinomatous meningitis is a metastatic cancer. The cancer cells that form tumors on the leptomeninges have come from other places in the body. Cancer cells break off from the primary tumor and circulate through the blood stream. When they enter the CSF, they act like seeds, attaching to many sites on the leptomeninges and developing into many tumors. The most common cancers that metastasize to carcinomatous meningitis are leukemia, **lymphoma**, **melanoma**, breast, lung, and **gastrointestinal cancers**.

Demographics

Once thought to be a rare complication of cancer, carcinomatous meningitis is increasing in frequency. This may be because people with cancer are living longer, giving the cancer a chance to spread to the central nervous system. The number of people who develop carcinomatous meningitis is difficult to determine. One study suggested that up to 8% of cancers become carcinomatous meningitis. Another small study published in 2000 found that 2% to 3% of women with **breast cancer** develop carcinomatous meningitis. Frequently, people who develop tumors in

KEY TERMS

Cerebrospinal fluid—Normal fluid found in the brain and around the central canal of the spinal cord.

Metastatic—Cancer that has spread from the original site (the primary tumor) to other parts of the body where secondary tumors are formed.

Magnetic resonance imaging (MRI)—A diagnostic tool that uses magnets and radio waves to create detailed cross-sectional pictures of the interior of the body.

the leptomeninges also develop them in other parts of the brain.

Causes and symptoms

Carcinomatous meningitis is caused by the spread of other types of cancer to the central nervous system. There are many symptoms, including:

- headache
- decrease in mental abilities
- confusion
- disturbances in the ability use the legs and arms
- back pain
- weakness
- burning or prickling sensations
- loss of feeling in the face
- problems with vision, hearing, or swallowing
- increased pressure in the brain due to the accumulation of fluid

Diagnosis

Magnetic resonance imaging (MRI) scans of the brain and spinal cord may be done as part of the diagnosis for carcinomatous meningitis. However, the definitive diagnosis comes from removing a sample of cerebrospinal fluid, looking at it under the microscope, and finding cancer cells. This procedure is called a **lumbar puncture**. It is common for doctors to have to do several lumbar punctures before a firm diagnosis can be made.

Treatment team

The treatment team for a patient with carcinomatous meningitis usually involves an oncologist (cancer specialist), possibly a surgeon, radiation oncologist (specialist in **radiation therapy**), radiation technicians, nurses with special training in cancer care, and a social worker.

Clinical staging, treatments, and prognosis

Carcinomatous meningitis is treated with either radiation or intrathecal **chemotherapy**. In radiation therapy, high-energy, penetrating waves or particles such as x rays, gamma rays, or proton rays are aimed at the spot where the tumor is located. The goal is to destroy the cancer cells or keep them from reproducing.

Intrathecal chemotherapy involves injecting chemotherapy drugs directly into the CSF. Drugs are injected either through a lumbar puncture or through an **Ommaya reservoir** located on the skull. The goal is for the drugs to kill the cancer cells, although some normal cells are also killed.

Carcinomatous meningitis is an advanced form of cancer that usually leads to degeneration of the nervous system and then to death. A person who has developed carcinomatous meningitis is likely to have tumors in other places in the body as well. The chance of recovery is very slight.

Alternative and complementary therapies

Alternative and complementary therapies range from herbal remedies, vitamin supplements, and special diets to spiritual practices, acupuncture, massage, and similar treatments. When these therapies are used in addition to conventional medicine, they are called complementary therapies. When they are used instead of conventional medicine, they are called alternative therapies.

No specific alternative therapies have been directed toward carcinomatous meningitis. However, good nutrition and activities, such as yoga, meditation, and massage, that reduce stress and promote a positive view of life have no unwanted side effects and may help improve the quality of life. Alternative and experimental treatments are usually not covered by insurance.

Coping with cancer treatment

Carcinomatous meningitis is usually fatal. In addition, radiation and chemotherapy cause **fatigue**, **nausea and vomiting**, and other uncomfortable side effects. Emotions are intense and often conflicting. In this extremely stressful time, it is often helpful for both the patient and loved ones to have the support of a therapist, religious leader, or other counselor. Hospice staff members or hospital social workers or chaplains can direct patients and family members to resources that address their individual needs.

QUESTIONS TO ASK THE DOCTOR

- What kind of changes in my body can I expect to see from this cancer?
- What is the treatment plan?
- What are the likely side effects of the treatment plan?
- How long am I likely to survive?

Clinical trials

In 2001, there were several **clinical trials** related to intrathecal chemotherapy treatment for carcinomatous meningitis. Current information on what clinical trials are available and where they are being held can be found by entering the search term "carcinomatous meningitis" at the following websites:

- National Cancer Institute <http://cancertrials.nci.nih.gov> or (800) 4-CANCER.
- National Institutes of Health Clinical Trials <http://clinicaltrials.gov>.
- Center Watch: A Clinical Trials Listing <http://www.centerwatch.com>.

Prevention

Carcinomatous meningitis arises from the spread of other cancers. The best form of prevention is immediate and thorough treatment of the primary cancer.

Resources

PERIODICALS

Martinelli, Giovanni, et al. "Intrathecal Chemotherapy in Carcinomatous Meningitis from Breast Cancer." *Annals of Oncology* 11, Supplement 4 (October 2000): 153.

ORGANIZATIONS

American Brain Tumor Association. 2720 River Road, Des Plaines, IL 60018. (847) 827-9910. Patient line (800) 886-2282. <http://www.abta.org>.

OTHER

Groerwald, Susan. "Brain & Central Nervous System Cancer: Brain Metastases." *cancersourceMD*. [cited February 14, 2000 and July 4, 2001]. <http://www.cancersourceMD.com>.

Tish Davidson, A.M.

Cardiomyopathy

Definition

Cardiomyopathy is a type of heart disease in which the heart muscle is abnormally enlarged, thickened and/or stiffened. As a result, the heart muscle's ability to pump blood is usually impaired.

Description

When the heart muscle enlarges and is unable to pump effectively, its function declines. This is called congestive heart failure. Congestive heart failure results in a reduction in oxygen delivery to the tissues and a backup of fluid into those tissues. Fluid in the lungs can cause shortness of breath with exertion and a need to sleep with the head elevated. Fluid buildup in other areas can manifest itself as swelling of the feet and ankles or swelling and pain in the liver. Congestive heart failure once carried a grim prognosis, but new advances in medical treatment have improved that prognosis significantly.

People with cardiomyopathy can develop an abrupt buildup of fluid in the lungs, called acute pulmonary edema. This is a medical emergency. In addition to intravenous medications that remove fluid, support blood pressure, and strengthen the heart's pumping function, acute pulmonary edema is also treated with oxygen and sometimes the temporary use of a respirator.

Almost anything that can damage the heart muscle fibers can produce cardiomyopathy and congestive heart failure. Long-standing high blood pressure, diabetes, heart attacks, alcohol, drugs, and certain viruses are all causes of cardiomyopathy.

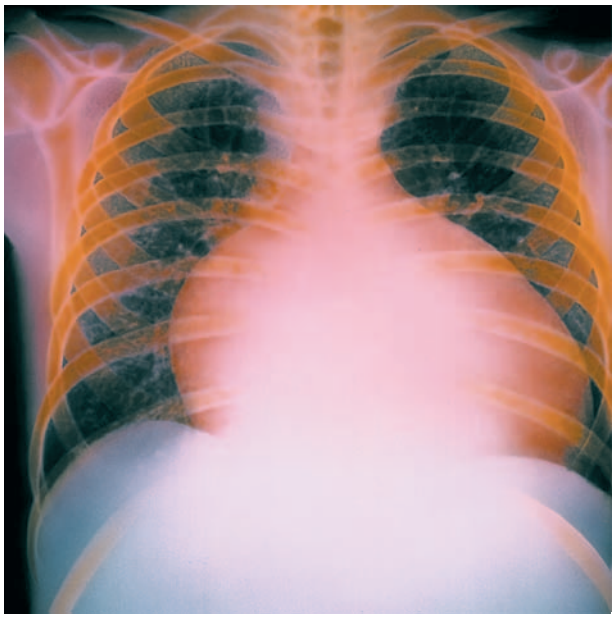
In a person with cancer, cardiomyopathy and its symptoms are generally due to the adverse effects of treatment.

Causes

Among the causes of cardiomyopathy in cancer patients is **radiation therapy** to the chest, which is often employed for **breast cancer**, cancer of the esophagus or **lymphoma**. Children who receive radiation therapy to the spinal column can suffer late effects to their hearts. The radiation can damage the heart muscle, leading to cardiomyopathy and heart failure. It can also damage the coronary arteries, leading to angina or a heart attack.

More commonly, cardiomyopathy in a cancer patient is an adverse effect of **chemotherapy**. Among the chemotherapeutic drugs known to be toxic to the heart are:

- **Doxorubicin**
- **Daunorubicin**



Colored chest x ray of a patient suffering from cardiomyopathy (heart failure), showing enlargement of the left ventricle of the heart. *(Photo Researchers, Inc. Reproduced by permission.)*

- **Mitoxantrone**
- **Cyclophosphamide**
- 5-Fluorouracil (**fluorouracil**)
- **Vincristine**
- **Vinblastine**
- **Busulfan**
- **Mitomycin C**
- **Cisplatin**
- **Amsacrine**
- **Paclitaxel**
- **Docetaxel**
- **Interferons**
- **Aldesleukin**
- **Trastuzumab**

The drugs most frequently associated with cardiotoxicity are doxorubicin and daunorubicin, which are anthracyclines. The total cumulative dose of anthracyclines a person receives determines the likelihood of developing chronic cardiomyopathy. In a few cases, these agents will cause an acute cardiotoxic effect, with symptoms such as abnormal heart rhythms and electrocardiogram changes.

Patients receiving anthracyclines have nuclear imaging scans of their hearts before starting treatment, during treatment and after treatment, since the adverse effects can be delayed. These studies measure the heart's ejection fraction, which is the percentage of blood volume pumped with each heartbeat. A normal ejection fraction is around 60%. In other words, 60% of the blood that collects in the heart between heartbeats is pumped out with each beat. Anthracyclines can cause a significant reduction in ejection fraction and therefore in heart function.

Often used for colon, breast, and **head and neck cancers**, 5-fluorouracil can cause cardiotoxicity, mostly in those patients with existing coronary artery disease or those who are also receiving radiation therapy to the chest. Cyclophosphamide, often used in those who have had bone marrow transplants, is another cause of cardiomyopathy. The taxanes, paclitaxel and docetaxel, are newer agents often used for breast and ovarian cancers. Taxanes can cause slowing of the heart rate, but this is not usually serious or prolonged.

Trastuzumab is a monoclonal antibody used in some patients with breast cancer. About 30% of women have overexpression of human epidermal growth factor receptors, called HER-2, on the surface of their cancer cells. Trastuzumab selectively attacks those receptors. Heart muscle also has some HER-2 receptors, which is believed to be the reason that trastuzumab can cause cardiomyopathy. Trastuzumab is often used in conjunction with anthracyclines or taxanes, both of which have effects on the heart, and patients on these drugs must be carefully monitored for signs of heart disease.

The diagnosis of cardiomyopathy is made on the basis of the history and physical examination, along with tests of heart function. Occasionally, biopsies of the heart muscle are performed to confirm the diagnosis.

Other forms of damage to the heart can occur with cancer and its treatments. Some cancers can metastasize to the heart muscle or the valves within the heart. Cancers that spread to the pericardium, the outer lining of the heart, can induce fluid collections called pericardial effusions.

High-output cardiac failure is an unusual form of heart failure that results when the body senses a lowered total blood volume. This can occur with **anemia**, a side effect of many treatments, or with large tumors that have large numbers of blood vessels, drawing blood away from the general circulation.

Amyloidosis is a condition in which abnormal proteins are deposited in tissues throughout the body, including the heart. Amyloidosis is seen with **multiple myeloma**.

Abnormal heart rhythms can occur due to toxic effects of chemotherapeutic drugs and perhaps radiation treatments on the electrical conducting system of the heart.

Treatments

The treatment of cardiomyopathy in cancer patients consists of removing the cause when possible and using cardiac medications to reduce symptoms.

Since the most common cause of cardiomyopathy in cancer patients is due to the use of anthracyclines, oncologists keep a careful record of the total dose administered to patients over the course of their treatment, and stop the drug before the known toxic dose has been reached.

Newer forms of anthracyclines have been formulated which are called liposome encapsulates. These have been shown to be less toxic to the heart and still effective against cancer. Administering anthracyclines weekly, rather than every three to four weeks, and giving the dose more slowly both seem to reduce the cardiac toxicity. The simultaneous administration of drugs that might protect the heart is under study, but their use is not yet recommended routinely.

The treatment of an established cardiomyopathy and heart failure due to cancer treatment is a combination of medications that are used for heart failure of any origin. One of these is digoxin, which improves the heart's pumping function in addition to other beneficial effects. Diuretics, often called water pills, flush water and salt from the body and are used to reduce swelling. Angiotensin-converting enzymes or ACE inhibitors comprise the third group of drugs useful for heart failure. These relax the arteries, which reduces the work that the heart must do to effectively pump blood. The fourth group of medications includes beta-blockers, which slow the heart rate and reduce its workload. This combination of medications has significantly improved the prognosis for people with heart failure.

Lifestyle changes can reduce symptoms of heart failure. Reducing salt and fluid intake and avoiding alcohol are beneficial. A judicious exercise plan can increase stamina without overtaxing a failing heart. Many people who have undergone cancer treatment also have coronary artery disease, which can aggravate the symptoms of heart failure caused by chemotherapy toxicity. Patients whose cancer prognosis is good can sometimes benefit from treatment of their coronary artery disease.

Some patients whose cancer is cured but whose cardiomyopathy progresses despite medication are candidates for heart transplant.

Alternative and complementary therapies

Naturopaths might prescribe hawthorn for symptoms of congestive heart failure. No studies have demonstrated either benefit or harm from this preparation.

Acupuncture and acupressure are sometimes beneficial in reducing symptoms of shortness of breath and may offer some relief to those with heart failure due to cardiomyopathy. The pressure point for the heart is said to be on the palm of the hand, over the bones between the fourth and fifth fingers.

KEY TERMS

Acute pulmonary edema—An abrupt collection of fluid in the lungs due to failure of the heart muscle to pump blood properly.

Angiotensin converting enzyme inhibitors—Medications that lower blood pressure and reduce the work load of the heart muscle.

Beta-blockers—Medications that relax blood vessels and slow the heart rate.

Congestive heart failure—A condition that results from inadequate pumping action of the heart muscle, causing fluid buildup in lungs and tissues.

Diuretics—Medications, often called water pills, that eliminate excess water and salts from the body.

Ejection fraction—The percentage of the blood sitting in the heart between heartbeats that gets pumped to the body with each heartbeat.

Resources

BOOKS

Moore, Katen, and Libby Schmais. *Living Well with Cancer: A Nurse Tells You Everything You Need to Know About Managing the Side Effects of Your Treatment*. New York: Putnam Publishing Group, 2001.

PERIODICALS

Ginsburg, A.D. "Doxorubicin-induced Cardiomyopathy." *New England Journal of Medicine* 340, no. 8 (February, 1999): 654.

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Marianne Vahey, M.D.

Carmustine

Definition

Carmustine is an antineoplastic drug, meaning that it inhibits the growth of cancer. It does this by disrupting DNA and synthesis, which leads to cell death. Carmustine is often referred to as BCNU, and along with other chemically similar drugs (**lomustine**, **semustine**, and **streptozocin**) is classified as a nitrosourea. Brand names for carmustine in the U.S. include BiCNU and Gliadel Wafers.

Purpose

Because it readily crosses the blood-brain barrier, carmustine is used to treat several types of brain tumors, including **astrocytoma**, **ependymoma**, glioblastoma, brainstem glioma, **medulloblastoma**. It is usually given intravenously, but it is also available as a wafer that is implanted in the brain during surgery. Carmustine is also used in the treatment of **multiple myeloma** and **melanoma**, usually in combination with other agents. It is also used in high does for patients undergoing bone marrow or stem cell transplants. Patients with non-Hodgkin's or Hodgkin's lymphoma whose disease has either relapsed or not responded to initial therapy, may be treated with carmustine used in combination with other drugs.

Description

Carmustine was approved for use by the U.S. Food and Drug Administration (FDA) in 1977. Carmustine comes in vial, in a powder form, and is reconstituted with sterile water according to the manufacturer's instructions. It may be used as a single agent, meaning it is administered alone; or it may be used with other drugs. It is further diluted in a larger volume of fluid and given slowly into a vein over a one- to two-hour period. Faster administration may cause a burning sensation in the vein, as well as facial flushing. The wafer is implanted surgically.

Carmustine is excreted by the kidneys during urination, and the lungs during expiration. Studies have shown that within four days, up to 70% of the drug is excreted in the urine, while an additional 10% is excreted in exhaled carbon dioxide. No one is certain what happens to the remaining 20% of the drug.

Recommended dosage

Because carmustine can have delayed toxic effects on the bone marrow, doses should be given at least four to six weeks apart. If carmustine is given in conjunction with other drugs that also suppress the bone marrow, dosages may be reduced. Blood tests are performed frequently during and after treatment, and their results may require dosage adjustments. Currently, there is no known remedy for a carmustine overdose.

Chemotherapy dosages are based on a person's body surface area (BSA), which is calculated in square meters using height and weight measurements. Drug dosages are ordered in milligrams per square meter (mg/m^2). Carmustine doses vary, but common doses include 75–250 mg/m^2 every four to six weeks, and 80 mg/m^2 daily for three days every six weeks. Higher doses are used for patients undergoing bone marrow or stem cell transplants. The specific dose should be verified for each patient. Continued doses after the first course of carmustine depend on the patient's response and on toxicity. Sometimes doses are adjusted because of toxicity or low blood counts.

Precautions

Carmustine may be damaging to an unborn fetus. Women of child-bearing potential should take measures to prevent pregnancy and women receiving carmustine should not breast-feed.

Side effects

Carmustine should be used after careful consideration of the risks and benefits involved, as there can be serious adverse side effects.

Myelosuppression

Effects on the bone marrow can lead to reduced numbers of platelets and white blood cells, which can have potentially life-threatening results, including bleeding and infection. These effects are first seen from four to six weeks after treatment is started, are cumulative, and are related to the amount of the drug given. A patient taking carmustine who develops a **fever** or notices an increased tendency to bleed or bruise may have dangerously low blood counts, and should be evaluated by a physician.

Pulmonary damage

Patients taking carmustine are at risk for damage to the lungs marked by pulmonary fibrosis. The main symptom of pulmonary fibrosis is shortness of breath. Pulmonary fibrosis can lead to heart failure. It is most likely to develop in patients with total cumulative doses greater than 1400 mg/m^2, although lower doses may also cause damage.

Individuals with underlying lung disease, such as chronic obstructive pulmonary disease, may be more likely to develop carmustine-associated pulmonary injury. Prior to initiating treatment with carmustine, a doctor will usually evaluate how well the lungs function by performing pulmonary function tests (PFTs). Patients are more likely to develop lung damage if portions of these tests are abnormal. PFTs may be repeated during treatment to monitor for adverse effects of carmustine. If carmustine is used in conjunction with other drugs that have toxic effects on pulmonary function, there may be a greater risk of lung damage.

Nausea and vomiting

Like many antineoplastic drugs, carmustine can cause **nausea and vomiting**. Before carmustine is administered, medications called **antiemetics** should be given to prevent or minimize nausea. Patients who experience severe nausea, or nausea that is uncontrolled with antiemetics, should notify their doctor.

Organ damage

Carmustine may cause damage to the kidneys. With careful monitoring and frequent blood tests, this damage can be prevented or reversed. Kidney damage is more likely to occur in individuals who have received prolonged therapy with large cumulative doses. Blood tests to evaluate renal function should be performed routinely. Carmustine may be discontinued or reduced depending on these results.

Secondary malignancies

Although carmustine is used to treat cancer, it may also cause secondary malignancies when used long term.

Carmustine wafers

Intracranial implantation of carmustine wafers has been associated with abnormal wound healing after surgery, brain edema or accumulation of fluid, infection, and the formation of cysts near the site of implantation.

Interactions

Patients should tell their doctor about medications they are taking in addition to their cancer treatment, as these medications may interact with carmustine. For example, cimetidine, a drug used to treat heartburn and ulcers, may increase the toxic effects of carmustine on the bone marrow. Carmustine, on the other hand, may decrease blood levels of **phenytoin**, a drug used in the treatment of patients with seizures. If blood levels are too low, seizures may not be prevented.

KEY TERMS

Antiemetic—A drug that prevents or alleviates nausea and vomiting.

Body surface area—A measurement based on height and weight that is expressed in square meters. It is used to determine chemotherapy dosages.

Myelosuppression—Suppression of bone marrow function that results in decreased platelets, red blood cells, and white blood cells.

Patients undergoing treatment for cancer with carmustine should talk to their doctor prior to taking any **vaccines**. Live vaccines, in particular, can increase the likelihood of complications.

Aspirin and ibuprofen, which are found in many over-the-counter products, should be avoided. These drugs can increase the potential for bleeding in people who may already have decreased platelet counts due to carmustine therapy.

Tamara Brown, R.N.

Cartilage supplements

Description

Cartilage is a type of dense connective tissue found in humans and other animals. Bluish-white or gray in color, the semi-opaque tissue has no nerve or blood supply of its own. Cartilage supplements come from such animal sources as cattle, sharks, sheep, and chickens, with cattle and sharks being the predominant sources. Bovine cartilage supplements are derived from the windpipes of cows, while the cartilage from the heads and fins of sharks is used for shark supplements.

General use

Both bovine and shark cartilage supplements have been proposed as treatments for cancer. In addition, a compound derived from cartilage called chondroitin has been publicized as a useful treatment for osteoarthritis. Cartilage preparations are available as pills, powders, or liquids for oral dosage. They can also be given as enemas, topical applications, or intravenous or intramuscular injections.

Bovine cartilage supplements

Beginning in the 1950s, the physician John F. Prudden noticed that bovine cartilage could enhance wound healing in animals. Prudden then injected an extract of bovine cartilage into a **breast cancer** patient whose tumor had ulcerated her skin. The patient's tumor ultimately disappeared, and she lived for 12 years before dying of other causes. In 1985, Prudden published the first of several scientific papers on the subject.

Prudden believed that the anticancer ingredients in bovine cartilage are mucopolysaccharides, which are complex sugar molecules that help fight cancer by stimulating the patient's immune system. Prudden also states that these large sugar molecules act on tumor cell membranes by blocking mitosis (cell division). Other proposed explanations of the effectiveness of bovine cartilage include the inhibition of protease, which is an enzyme that helps to break down proteins, and inhibited formation of enzymes that break down collagen proteins. Numerous bovine cartilage supplements have been made available for immuno-stimulation or to fight off cancer cells. Most reports on tumor response and the survival of cancer patients after cartilage treatment, however, are anecdotal.

In 2001, researchers at Georgetown University in Washington D.C. reported on the isolation of a compound, which they named *metastatin*, from bovine cartilage. Metastatin was able to block the formation of tumor nodules in the lungs of mice inoculated with b16bl6 **melanoma** or Lewis lung **carcinoma** cells. They concluded that metastatin is a potentially useful antitumor agent. Variations in study results may, in part, be due to variations in concentration and availability of metastatin.

Shark cartilage supplements

The use of shark cartilage to treat cancer is based on the claim that it blocks angiogenesis, or the development of new blood vessels that tumors need to survive. A researcher at Harvard Medical School in the 1970s, Judah Folkman, developed the theory of angiogenesis. Folkman's proposal that tumors, much like a normal organ or mass of cells, require a supply of blood to deliver nutrients for growth, has since become closely linked to the treatment of cancer with shark cartilage.

In 1983, William Lang, motivated by Folkman's research, began investigating the possible link between shark cartilage and its ability to starve tumors with an anti-angiogenetic mechanism. In 1993, Lane published his book *Sharks Don't Get Cancer*, making shark cartilage one of the leading alternative cancer therapies, with 99% of the cartilage market in 1997 comprised of shark cartilage.

The use of shark cartilage as an alternative treatment has been opposed by wildlife experts who say that use of the substance threatens the shark population. A study discussed at a cancer research meeting in 2000 documented about a dozen cases of apparent cancer in sharks, including cancer of the cartilage.

Both shark and bovine cartilage have been used to treat a wide variety of cancers, including tumors of the breast, ovary, cervix, prostate, rectum, colon, stomach, kidney, and brain. The U.S. Food and Drug Administration (FDA) maintains that both types of cartilage can be tested as potential cancer therapy in **clinical trials** but must be sold strictly as dietary supplements. Dietary supplement manufacturers as of 2005 are also prohibited from making specific claims that the supplements can cure disease.

Chondroitin sulfate

Chondroitin is best known to the general public as a remedy for osteoarthritis, which is a form of arthritis caused by wearing away or degeneration of the cartilage that cushions the ends of bones. It is thought that the drying out of cartilage tissue in osteoarthritis is a major cause of tissue destruction. Chondroitin sulfate is given together with glucosamine, a compound that is a building block of cartilage. The chondroitin helps to attract and hold fluid within cartilage tissue. Tissue fluid keeps cartilage healthy in two ways: it acts as a shock absorber within the joints of the body, thus protecting cartilage from being worn away by the bones, and it carries nutrients to the cartilage. A 2001 study showed that combining glucosamine and chondroitin worked better than either alone in preventing cartilage damage and that both supplements worked well when taken orally.

Preparations

Shark and bovine cartilage supplements are available in capsule form, while shark is also sold as a powder and liquid. Shark supplements are made from ground-up shark skeletons (mainly the fins and head), while bovine supplements are prepared from the cartilage taken from cow bones. Chondroitin sulfate can be taken orally as a pill, powder, or liquid. It can also be administered by injection. Oral preparations of chondroitin, by itself or in combination with glucosamine, are available in the United States as over-the-counter (OTC) dietary supplements. They can be purchased over the Internet, at pharmacies, health food stores, or even some grocery stores.

Precautions

While cartilage supplements do not appear to be harmful, persons who are considering them as a cancer

KEY TERMS

Angiogenesis—The development of new blood vessels, specifically those that supply tumors with blood and nutrients for growth.

Chondroitin—A complex carbohydrate found in human and animal cartilage that is used to treat several physical disorders, most importantly arthritis.

Glucosamine—A complex carbohydrate composed of glucose and an amino acid called glutamine. It is an important building block of cartilage and is often taken together with chondroitin as a treatment for osteoarthritis.

Mucopolysaccharide—An older term for a class of large sugar molecules that are found in cartilage and other forms of connective tissue. Mucopolysaccharides are now called glycosaminoglycans.

treatment should not use them as their sole form of therapy and should consult their doctor before taking them. Persons who are considering chondroitin as a treatment for joint pain should be careful not to diagnose themselves. They should check with their physician to be sure that the pain is caused by osteoarthritis. Some conditions, including Lyme disease, gout, bursitis, and rheumatoid arthritis, can also cause pain in the joints. Although chondroitin appears to be helpful in treating osteoarthritis, it is not useful for these other conditions. Chondroitin has not been studied in children or in pregnant or nursing women.

Side effects

Both shark and bovine cartilage supplements show little or no side effects when taken at the appropriate dosage levels. Some patients have reported an allergic reaction to traces of bovine protein or other side effects that include a bad taste in the mouth, **fatigue**, and nausea. Shark cartilage can cause **hypercalcemia** (excessive amounts of calcium in the body) when taken at the recommended daily dose of 70 g per day, 14 times the amount of calcium recommended by the United States Recommended Daily Allowance (USRDA). Some patients taking chondroitin have been known to experience nausea and gas or bloating.

Interactions

Chondroitin sulfate is not known to cause any significant interactions with other medications.

Resources

PERIODICALS

Theodosakis, Jason. "Relief for your Painful Joints (Wellness)." *Better Nutrition* (May 2002): 32.

ORGANIZATIONS

National Cancer Institute Cancer Information Service (CIS). (800)332-8615. <http://www.cancernet.nci.nih.gov>.

NIH National Center for Complementary and Alternative Medicine (NCCAM). NCCAM Clearinghouse. PO Box 8218, Silver Spring, MD 20907-8218. (888)644-6226. <www.nccam.nih.gov/nccam>.

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CAT scan, CT scan, Computerized axial tomography *see* **Computed tomography**

Cefepime *see* **Antibiotics**

Ceftazidime *see* **Antibiotics**

Ceftriaxone *see* **Antibiotics**

Celecoxib *see* **Cyclooxygenase 2 inhibitors**

Cellcept *see* **Mycophenolate mofetil**

Central nervous system carcinoma

Definition

A central nervous system **carcinoma** is a malignant tumor arising in the cells of the brain or spinal cord.

Description

The central nervous system (CNS) is comprised of the brain and spinal cord. The CNS takes its name from the crucial role it plays in maintaining physical and mental well-being (homeostasis). The brain controls and monitors the body's activity; the spinal cord conveys information to the body from the brain, and vice versa.

Consequently, a tumor in the CNS disrupts motor (e.g., standing, walking, writing) and sensory (e.g., seeing, tasting, hearing) activities.

The two major components of brain tissue are neurons (nerve cells) and glial cells. About half of all malignant CNS tumor growth starts in glial cells. Long thought to be mere space-holders, glial cells have been found to be extremely important. These cells actually protect and nourish the neurons, and may also help them transmit information. There are many different types of glial carcinomas, or gliomas.

The three layers of membrane (meninges) that cover the brain and spinal cord and the pituitary and pineal parts of the brain, are common sites for tumor growth. About 40% of benign (noncancerous) CNS tumors occur in the meninges and the pituitary and pineal glands.

Some cancers that originate in organs, such as the kidneys, spread (metastasize) to the brain and spinal cord. These metastases differ from CNS carcinomas, however.

Demographics

About 35,000 cases of CNS carcinoma are diagnosed each year. The Central Brain Tumor Registry of the United States (CBTRUS) puts the incidence of CNS tumors at 12.8 per 100,000 person-years. The rate is slightly higher in males and slightly lower in females. Over a lifetime the chance a man will be diagnosed with and die from a CNS tumor is 1 in 200 and for a woman the rate is 1 in 263.

The older a person is the more likely he or she is to be diagnosed with CNS carcinoma. According to CBTRUS, the pediatric (individuals ages 0-19 years) incidence of CNS tumors is significantly lower, or about 3.8 per 100,000 person-years. People under the age of 20 years also have a higher survival rate. They are five times more likely to live at least five years with a CNS tumor than are people between the ages of 45 and 64 years.

In addition to the diagnosis of primary CNS tumors (those that originate in the brain and spinal cord) is the diagnosis of metastatic cancer. Metastatic cancers are those that have spread from other primary sites, such as the breast, prostate, lungs, and colon. For every person diagnosed with a primary CNS tumor, at least four other individuals will be diagnosed with cancer that has metastasized to the brain and spinal cord. Occasionally, the identification of a metastatic brain cancer leads a physician to discover a cancer in another organ, or the **primary site**.

Causes and symptoms

The cause of CNS carcinoma is unknown. Important factors might include heredity, genetic make-up, and exposure to radiation and chemicals. Head injury might lead to meningiomas (carcinoma of the meninges). Extra or missing chromosomes or other genetic abnormalities are linked to the development of some CNS tumors. In 2004, researchers identified a gene that may be linked to development of gliomas, the most common type of brain tumor. In one study a group of researchers led by T. Ballard showed pilots and flight attendants are at greater risk for CNS carcinoma, perhaps because of their frequent exposure to high levels of cosmic radiation.

Many individuals display no symptoms of CNS carcinoma until the tumor has grown large enough to exert pressure on part of the CNS. Because the skull covers the brain and the vertebral column protects the spinal cord, a growing tumor soon pushes up against a barrier of bone. The bone limits the expansion of the tumor and the cancerous and adjacent parts of the CNS become distorted. The meninges then swell in response to the distortion, producing symptoms.

Symptoms include:

- headache
- muscle weakness
- exhaustion
- **nausea and vomiting**
- changes in vision
- seizures

When a tumor is in the spinal cord, symptoms include back pain and **incontinence** (inability to control defecation and urination). Paralysis on one side of the body (hemiparesis), which often indicates a stroke in an elderly person, sometimes occurs because of a brain tumor.

Diagnosis

Seizures and difficulties with walking, speech, sight, or other day-to-day activities usually cause patients with CNS carcinoma to consult a physician. The techniques a physician uses to diagnose CNS carcinoma begin with an examination and medical history. Some combination of blood tests, **x ray**, **computed tomography** (CT), and **magnetic resonance imaging** (MRI) is used. In recent years, another form of imaging called positron emission tomography, (PET) has been used increasingly to diagnose and monitor treatment of CNS carcinoma and other cancers. If a tumor is detected with a CT or MRI scan a **biopsy** is usually done to determine the type of tumor.

Treatment team

A CNS carcinoma requires attention from several different types of physician specialists. A neurologist, a physician specializing in the nervous system, does the initial assessment. A radiologist interprets x rays, CT and MRI images. A hematologist or oncologist evaluates the results of blood tests. A pathologist studies the tissue from a biopsy. The surgery team typically is led by a neurosurgeon. At premier cancer centers teams of physicians work collaboratively with one person, usually an oncologist, taking the lead. Physical and occupational therapists help with rehabilitation following treatment and surgery, and registered nurses who administer **chemotherapy**, are also part of the team.

Clinical staging, treatments, and prognosis

By studying tissue from the tumor and surrounding cells the oncologist determines whether the tumor is growing and, if so, how fast. A precise system assigns stages and grades to the tumors. Staging and grading helps physicians compare cases, monitor treatment and determine prognosis. Staging depends on things such as which part of the brain was served by the glial cell(s) in which the tumor began.

A plan for treatment is based on the location, size, and rate of growth of the tumor. Surgical removal of the tumor, radiation, and chemotherapy are all used. Method of treatment depends on the type of CNS carcinoma. In some cases the treatment is strictly palliative (provides comfort) and is not expected to halt the course of the cancer. Drugs, such as steroids, are often given to reduce swelling and, correspondingly, reduce pain and other symptoms.

About three-fourths of all individuals diagnosed with CNS carcinoma die before attaining a five-year survival rate.

Alternative and complementary therapies

Relaxation techniques may help to relieve pain from swelling.

Coping with cancer treatment

Being an active participant in the treatment team, something that specialized cancer centers encourage, is one way to cope. Joining a support group also may help.

Clinical trials

The National Cancer Institute at the National Institutes of Health operates an information service that provides the most up-to-date information about **clinical trials**. The number is (800) 4-CANCER ([800] 422-6237).

KEY TERMS

Biopsy—Tissue sample taken from body for microscopic examination.

Carcinoma—A cancer that originates in cells that developed from epithelial tissue, a tissue that forms layers and often specializes to cover and protect organs.

Computed tomography (CT)—X rays aimed at sections of the body (by rotating equipment). The images appear as slices. Results are assembled with a computer to give a three-dimensional image.

Homeostasis—Self-regulating mechanisms are working, body is in equilibrium, no uncontrolled cell growth.

Magnetic resonance imaging (MRI)—Magnetic fields and radio frequency waves are used to make images of the inside of the body.

Meninges—The three layers of tissue that cover the brain and spinal cord.

Pineal—A very small gland in the center of the brain that is sensitive to light.

Pituitary—A gland at the base of the brain that produces hormones.

Positron emission tomography (PET)—A nuclear medicine procedure in which small amounts of radioactive materials are placed in the patient's body, usually by injection. Then a special camera and computer reconstruct a three-dimensional image.

Prevention

Limiting exposure to cosmic radiation and chemicals might lower the risk. However, experts have no specific recommendations for prevention.

Special concerns

Psychological changes as simple as mood swings and as severe as major changes in personality are possible. Sensory impairment is also possible. **Advance directives**, or written instructions for the care a person wants at each juncture of treatment should be prepared and legalized as early in the therapeutic process as possi-

QUESTIONS TO ASK THE DOCTOR

- Which type of CNS carcinoma do I have?
- With this type of carcinoma, what is the five-year survival rate for a person of my age and gender? What is the one-year survival rate?
- Is there a center that specializes in treating this type of cancer?
- Are there any clinical trials in which I might be eligible to participate?
- Does this health care institution have a support group for individuals with my type of carcinoma?
- What is your approach to relieving pain? (Do we agree?)

ble. Such directives make the patient's choices clear should he or she become unable to express them as the cancer progresses. Doing so relieves loved ones of the responsibility for making those decisions, which can become extremely difficult.

See also Brain and central nervous system tumors.

Resources

PERIODICALS

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Huncharek, M., et al. "Chemotherapy Response Rates in Recurrent/Progressive Pediatric Glioma; Results of a Systematic Review." *Anticancer Research* 19 (July-August 1999): 3569-74.

ORGANIZATIONS

American Brain Tumor Association. 2720 River Road, Des Plaines, IL 60018 (800) 886-2282 <http://www.abta.org>.

The Brain Tumor Society. 124 Watertown Street, Suite 3-H, Watertown, MA 02472. (617) 924-9997 <http://www.tbts.org>.

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Central nervous system lymphoma

Definition

Central nervous system (CNS) lymphoma is a malignant growth, or neoplasm, that originates in the white blood cells of the lymphatic fluid in the brain and spinal cord.

Description

CNS lymphoma affects the brain and the spinal cord, the two components of the CNS. The brain and spinal cord work together to control, monitor, and interpret all the physical and mental processes of the body. They make possible the activities a person takes for granted, such as walking, talking, thinking, and remembering. A malignancy, or neoplasm, in the brain or spinal cord interferes with the normal functions of the body.

An uncontrolled growth of cells called lymphocytes causes lymphoma. Lymphocytes are the white blood cells in the lymphatic system. Under normal conditions they help the body resist invasion by foreign substances and organisms. In other words, they assist with **immune response** or defense.

When the uncontrolled growth of lymphocytes originates in the brain or spinal cord, it is called primary CNS lymphoma, or simply, CNS lymphoma. The specific place of origin of CNS lymphoma is probably in cells known as B cells. Other kinds of lymphoma begin elsewhere in the lymphatic system. They may also eventually affect the brain and spinal cord, but they are not called CNS lymphoma.

In most cases, CNS lymphoma does not produce a defined and specific site of growth, or a tumor. Generally, the cancer cells spread throughout the brain and spi-

nal cord. The spread gives way to lesions, which are places where tissue breaks down.

Demographics

Although the number of cases is on the increase, CNS lymphoma is rare. Between 1 and 2% of all uncontrolled growths in the brain result from CNS lymphoma. The most common age of diagnosis in the general population is between 52 and 55 years. However, in patients who have experienced immune system problems, age at diagnosis is much younger, at about 34 years.

Events and conditions that affect the immune system put a person at greater risk for CNS lymphoma. For example, someone who has had an organ transplant is more vulnerable to the disease. Part of the reason is that transplant patients are given drugs to suppress, or reduce, the action of the immune system so their bodies will accept an organ from a donor. Individuals with acquired immunodeficiency syndrome (AIDS) are also at higher risk for CNS lymphoma.

Causes and symptoms

The cause of CNS lymphoma is not known. It is more common in individuals with suppressed immune systems, and individuals with some conditions linked to the X chromosome, one of the two sex chromosomes, seem to be at higher risk. Studies indicate that exposure to certain herbicides also increases risk.

One role of the lymphatic system is to collect fluid that builds up outside cells and to return it to blood vessels. CNS lymphoma obstructs this process. Fluid builds up in the body and puts particular pressure on the cranial nerves, the nerves that carry information directly from the brain to organs such as the eyes and ears. Consequently, symptoms of CNS lymphoma often occur in the organs of the head and in the face.

Symptoms include:

- change in personality
- headache
- **nausea and vomiting**
- seizures
- weakness
- numbness, particularly in the face
- sensory problems (cannot hear, see)
- difficulty swallowing

Diagnosis

Symptoms cause a person to consult a physician. The initial assessment is made using **computed tomography** (CT) or **magnetic resonance imaging** (MRI). To confirm a diagnosis a physician does a variety of tests. They include a physical examination of lymph nodes, chest **x ray**, blood and urine tests, eye exam, bone marrow **biopsy**, and—in males—an ultrasound of the testes. Some of the tests are done to rule out other kinds of lymphoma.

KEY TERMS

B lymphocyte—Cell in the lymph system that produces antibodies, which protect against foreign substances.

Biopsy—Tissue sample taken from the body for microscopic examination.

Computed tomography (CT)—X rays are aimed at sections of the body (by rotating equipment) and images appear as slices. Results are assembled with a computer to give a three-dimensional picture of a structure within the body.

Herbicide—A chemical compound used to kill plants.

Lymphatic system—The nodes of tissue and the fluid that moves among them. This system works to protect the body from invading substances and organisms, and to return fluid that collects outside cells to the blood vessels.

Magnetic resonance imaging (MRI)—Magnetic fields and radio frequency waves take pictures (images) of the inside of the body.

Ultrasound—Sound waves are bounced off structures in the body to produce an image of those structures.

Treatment team

CNS lymphoma requires attention from several different types of physician specialists. A neurologist—a physician specializing in the nervous system—does the initial assessment. A radiologist interprets x rays, CT scans, and MRI images. A hematologist or oncologist evaluates the results of blood tests. A pathologist studies the tissue from a biopsy. If there is surgery, and in many cases there is not, a surgery team removes the tumor. At premier cancer centers, teams of physicians work collaboratively, with one person (usually an oncologist) taking the lead. Physical and occupational therapists help with rehabilitation following treatment and surgery, and registered nurses who administer **chemotherapy**, are also part of the team.

QUESTIONS TO ASK THE DOCTOR

- Will my quality of life be better with or without radiation treatment? How much of the time that I gain from radiation treatment will be time that I can function and do some of the things I enjoy?
- Is there a clinical trial in which I could participate?
- Is there a support group for CNS lymphoma at this institution or in this town?

Clinical staging, treatments, and prognosis

Treatment is primarily palliative (designed to provide relief from symptoms and make a patient comfortable). Surgery is sometimes used to eliminate well-defined masses that are causing pressure in the brain and spinal cord. This pressure causes the symptoms, such as headache and numbness, because it contributes to swelling and dislocation. However, because CNS lymphoma generally spreads throughout the brain and spinal cord, surgery is usually not a treatment choice.

Medication in the form of steroids and radiation treatment both give good results over the short term by causing clusters of malignant cells to shrink briefly. However, neither treatment is effective for much more than six months. A great deal of interest surrounds research aimed at finding chemotherapy that works effectively for this type of cancer. Chemotherapy for CNS lymphoma is sometimes given by putting drugs directly into the brain or spinal cord.

The prognosis (outlook for recovery) for a patient with CNS lymphoma is poor. Untreated, the disease usually results in death in just a few weeks. If it is treated, life can be extended by perhaps six months to one year, and occasionally longer. Those who survive CNS lymphoma for some time may face problems with cognitive function (ability to think and reason) that likely is related to treatment, probably radiation to the area.

Ulrich Herrlinger, M.D., and colleagues in Tuebingen, Germany, have reported that the combination of **radiation therapy** and chemotherapy gives patients a much better chance of extended survival, prolonging life for more than six years in one individual. Eleven of the 21 patients in their study lived for 33 months or longer.

Alternative and complementary therapies

Any relaxation program, such as biofeedback or yoga, often help a patient deal with the poor prognosis, pain, and symptoms of CNS lymphoma.

Coping with cancer treatment

Radiation therapy, particularly of the entire brain that is required to treat most CNS lymphoma, can greatly alter memory and thought processes. Being prepared for the effects of radiation before the treatment begins is important. For example, a patient can write out a daily schedule of things to do—the essentials of an ordinary day such as brushing teeth and combing hair. This schedule can then be used as a memory aid after treatment.

Having a patient taking an active part in planning the course of treatment can be helpful, such as participating in meetings with the treatment team. Premier cancer treatment centers encourage patients to be an integral member of the team. Because some individuals beat the odds and live much longer than expected, an optimistic attitude is important.

Clinical trials

The National Cancer Institute at the National Institutes of Health, Bethesda, MD, offers a Cancer Information Service that can connect people with **clinical trials**. The toll free number for the Service is 1-800-4-CANCER (1-800-422-6237).

Prevention

No prevention is known; however, any effort that reduces the number of people infected with the virus that causes AIDS will indirectly reduce the number of people with CNS lymphoma. Three percent of all AIDS patients exhibit CNS lymphoma.

Special concerns

Because CNS lymphoma is a fatal disease, patients must make decisions about end-of-life care. How will it be arranged: at home, in a hospice, in some other setting? Who will make decisions if the patient is no longer able to state his or her desires? **Advance directives**, or written instructions for how a person wishes the medical team to respond at each juncture of the illness, should be completed as soon as possible after a diagnosis is made.

Resources

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Central nervous system tumors *see* **Brain/Central nervous system tumors**

Cerebrospinal fluid analysis, spinal tap *see* **Lumbar puncture**

Cervical cancer

Definition

Cervical cancer is a disease in which the cells of the cervix become abnormal and start to grow uncontrollably, forming tumors.

Description

In the United States, cervical cancer is the fifth most common cancer among women aged 35-54, and the third most common cancer of the female reproductive tract. In some developing countries, it is the most common type of cancer. It generally begins as an abnormality in the cells on the outside of the cervix. The cervix is the lower part or neck of the uterus (womb). It connects the body of the uterus to the vagina (birth canal).

Approximately 90% of cervical cancers are squamous cell carcinomas. This type of cancer originates in the thin, flat, squamous cells on the surface of the ectocervix, the part of the cervix that is next to the vagina. (Squamous cells are the thin, flat cells of the surfaces of the skin and cervix and linings of various organs.) Another 10% of cervical cancers are of the adenocarcinoma type. This cancer originates in the mucus-producing cells of the inner or endocervix, near the body of the uterus. Occasionally, the cancer may have characteristics of both types and is called adenosquamous **carcinoma** or mixed carcinoma.

The initial changes that may occur in some cervical cells are not cancerous. However, these precancerous cells form a lesion called dysplasia or a squamous intraepithelial lesion (SIL), since it occurs within the epithelial or outer layer of cells. These abnormal cells can also be described as cervical intraepithelial neoplasia (CIN). Moderate to severe dysplasia may be called carcinoma in situ or non-invasive cervical cancer.

Dysplasia is a common condition and the abnormal cells often disappear without treatment. However, these precancerous cells can become cancerous. This may take years, although it can happen in less than a year. Eventually, the abnormal cells start to grow uncontrollably into the deeper layers of the cervix, becoming an invasive cervical cancer.

Although cervical cancer used to be one of the most common causes of cancer death among American women, in the past 40 years there has been a 75% decrease in mortality. This is primarily due to routine screening with Pap tests (Pap smear), to identify precancerous and early-invasive stages of cervical cancer. With treatment, these conditions have a cure rate of nearly 100%.

Demographics

Worldwide, there are more than 400,000 new cases of cervical cancer diagnosed each year. The American Cancer Society (ACS) estimated 13,000 new cases of invasive cervical cancer in the United States in 2002. More than one million women were diagnosed with a precancerous lesion or non-invasive cancer of the cervix in 2001.

Older women are at the highest risk for cervical cancer. Although girls under the age of 15 rarely develop this cancer, the risk factor begins to increase in the late teens. Rates for carcinoma in situ peak between the ages of 20 and 30. In the United States, the incidence of invasive cervical cancer increases rapidly with age for African-American women over the age of 25. The incidence rises more slowly for Caucasian women. However women over age 65 account for more than 25% of all cases of invasive cervical cancer.

The incidence of cervical cancer is highest among poor women and among women in developing countries. In the United States, the death rates from cervical cancer are higher among Hispanic, Native American, and African American women than among Caucasian women. These groups of women are much less likely to receive regular Pap tests. Therefore, their cervical cancers usually are diagnosed at a much later stage, after the cancer has spread to other parts of the body.

Causes and symptoms

Human papillomavirus

Infection with the common **human papillomavirus** (HPV) is a cause of approximately 90% of all cervical cancers. There are more than 80 types of HPV. About 30 of these types can be transmitted sexually, including

those that cause genital warts (papillomas). About half of the sexually transmitted HPVs are associated with cervical cancer. These "high-risk" HPVs produce a protein that can cause cervical epithelial cells to grow uncontrollably. The virus makes a second protein that interferes with tumor suppressors that are produced by the human immune system. The HPV-16 strain is thought to be a cause of about 50% of cervical cancers.

More than six million women in the United States have persistent HPV infections, for which there are no cure. Nevertheless, most women with HPV do not develop cervical cancer.

Symptoms of invasive cervical cancer

Most women do not have symptoms of cervical cancer until it has become invasive. At that point, the symptoms may include:

- unusual vaginal discharge
- light vaginal bleeding or spots of blood outside of normal menstruation
- pain or vaginal bleeding with sexual intercourse
- post-menopausal vaginal bleedingOnce the cancer has invaded the tissue surrounding the cervix, a woman may experience pain in the pelvic region and heavy bleeding from the vagina.

Diagnosis

The Pap test

Most often, cervical cancer is first detected with a **Pap test** that is performed as part of a regular pelvic examination. The vagina is spread with a metal or plastic instrument called a speculum. A swab is used to remove mucus and cells from the cervix. This sample is sent to a laboratory for microscopic examination.

The Pap test is a screening tool rather than a diagnostic tool. It is very efficient at detecting cervical abnormalities. The Bethesda System commonly is used to report Pap test results. A negative test means that no abnormalities are present in the cervical tissue. A positive Pap test describes abnormal cervical cells as low-grade or high-grade SIL, depending on the extent of dysplasia. About 5-10% of Pap tests show at least mild abnormalities. However, a number of factors other than cervical cancer can cause abnormalities, including inflammation from bacteria or yeast infections. A few months after the infection is treated, the Pap test is repeated.

Biopsy

Following an abnormal Pap test, a colposcopy is usually performed. The physician uses a magnifying scope to view the surface of the cervix. The cervix may be coated with an iodine solution that causes normal cells to turn brown and abnormal cells to turn white or yellow. This is called a Schiller test. If any abnormal areas are observed, a colposcopic **biopsy** may be performed. A biopsy is the removal of a small piece of tissue for microscopic examination by a pathologist.

Other types of cervical biopsies may be performed. An endocervical curettage is a biopsy in which a narrow instrument called a curette is used to scrape tissue from inside the opening of the cervix. A cone biopsy, or conization, is used to remove a cone-shaped piece of tissue from the cervix. In a cold knife cone biopsy, a surgical scalpel or laser is used to remove the tissue. A loop electrosurgical excision procedure (LEEP) is a cone biopsy using a wire that is heated by an electrical current. Cone biopsies can be used to determine whether abnormal cells have invaded below the surface of the cervix. They also can be used to treat many precancers and very early cancers. Biopsies may be performed with a local or general anesthetic. They may cause cramping and bleeding.

Diagnosing the stage

Following a diagnosis of cervical cancer, various procedures may be used to stage the disease (determine how far the cancer has spread). For example, additional pelvic exams may be performed under anesthesia.

There are several procedures for determining if cervical cancer has invaded the urinary tract. With **cystoscopy**, a lighted tube with a lens is inserted through the urethra (the urine tube from the bladder to the exterior) and into the bladder to examine these organs for cancerous cells. Tissue samples may be removed for microscopic examination by a pathologist. **Intravenous urography** (intravenous pyelogram or IVP) is an **x ray** of the urinary system, following the injection of special dye. The kidneys remove the dye from the bloodstream and the dye passes into the ureters (the tubes from the kidneys to the bladder) and bladder. IVP can detect a blocked ureter, caused by the spread of cancer to the pelvic lymph nodes (small glands that are part of the immune system).

A procedure called proctoscopy or **sigmoidoscopy** is similar to cystoscopy. It is used to determine whether the cancer has spread to the rectum or lower large intestine.

Computed tomography (CT or CAT) scans, ultrasound, or other imaging techniques may be used to determine the spread of cancer to various parts of the body. With a CT scan, an x-ray beam rotates around the body, taking images from various angles. It is used to determine if the cancer has spread to the lymph nodes.

Magnetic resonance imaging (MRI), which uses a magnetic field to image the body, sometimes is used for evaluating the spread of cervical cancer. Chest x rays may be used to detect cervical cancer that has spread to the lungs.

Treatment team

Pap smears usually are performed by a women's health specialist, a nurse practitioner, a family practice physician, or a gynecologist. These practitioners may treat precancerous conditions. Procedures for diagnosing cervical cancer are performed by a gynecologist. A pathologist examines the biopsied tissue for cancer cells. Following diagnosis, a specialist in cancers of the female reproductive system, a gynecological oncologist, as well as a radiation oncologist and a surgeon may join the team.

Clinical staging, treatments, and prognosis

Following a diagnosis of cervical cancer, the physician takes a medical history and performs a complete physical examination. This includes an evaluation of symptoms and risk factors for cervical cancer. The lymph nodes are examined for evidence that the cancer has spread from the cervix. The choice of treatment depends on the clinical stage of the disease.

The FIGO system of staging

The International Federation of Gynecologists and Obstetricians (FIGO) system usually is used to stage cervical cancer:

- Stage 0: Carcinoma in situ; non-invasive cancer that is confined to the layer of cells lining the cervix.
- Stage I: Cancer that has spread into the connective tissue of the cervix but is confined to the uterus.
- Stage IA: Very small cancerous area that is visible only with a microscope.
- Stage IA1: Invasion area is less than 3 mm (0.13 in) deep and 7 mm (0.33 in) wide.
- Stage IA2: Invasion area is 3–5 mm (0.13-0.2 in) deep and less than 7 mm (0.33 in) wide.
- Stage IB: Cancer can be seen without a microscope or is deeper than 5 mm (0.2 in) or wider than 7 mm (0.33 in).
- Stage IB1: Cancer is no larger than 4 cm (1.6 in).
- Stage IB2: Stage IB cancer is larger than 4 cm (1.6 in).
- Stage II: Cancer has spread from the cervix but is confined to the pelvic region.
- Stage IIA: Cancer has spread to the upper region of the vagina, but not to the lower one-third of the vagina.
- Stage IIB: Cancer has spread to the parametrial tissue adjacent to the cervix.
- Stage III: Cancer has spread to the lower one-third of the vagina or to the wall of the pelvis and may be blocking the ureters.
- Stage IIIA: Cancer has spread to the lower vagina but not to the pelvic wall.
- Stage IIIB: Cancer has spread to the pelvic wall and/or is blocking the flow of urine through the ureters to the bladder.
- Stage IV: Cancer has spread to other parts of the body.
- Stage IVA: Cancer has spread to the bladder or rectum.
- Stage IVB: Cancer has spread to distant organs such as the lungs.
- Recurrent: Following treatment, cancer has returned to the cervix or some other part of the body.

In addition to the stage of the cancer, factors such as a woman's age, general health, and preferences may influence the choice of treatment. The exact location of the cancer within the cervix and the type of cervical cancer also are important considerations.

Treatment of precancer and carcinoma in situ

Most low-grade SILs that are detected with Pap tests revert to normal without treatment. Most high-grade SILs require treatment. Treatments to remove precancerous cells include:

- cold knife cone biopsy
- LEEP
- cryosurgery (freezing the cells with a metal probe)
- cauterization or diathermy (burning off the cells)
- laser surgery (burning off the cells with a laser beam)

These methods also may be used to treat cancer that is confined to the surface of the cervix (stage 0) and other early-stage cervical cancers in women who may want to become pregnant. They may be used in conjunction with other treatments. These procedures may cause bleeding or cramping. All of these treatments require close follow-up to detect any recurrence of the cancer.

Surgery

A simple hysterectomy is used to treat some stages O and IA cervical cancers. Usually only the uterus is removed, although occasionally the fallopian tubes and ovaries are removed as well. The tissues adjoining the uterus, including the vagina, remain intact. The uterus may be removed either through the abdomen or the vagina.

In a radical hysterectomy, the uterus and adjoining tissues, including the ovaries, the upper region (1 in) of the vagina near the cervix, and the pelvic lymph nodes, are all removed. A radical hysterectomy usually involves abdominal surgery. However it can be performed vaginally, in combination with a laparoscopic pelvic **lymph node dissection**. With **laparoscopy**, a tube is inserted through a very small surgical incision for the removal of the lymph nodes. These operations are used to treat stages IA2, IB, and IIA cervical cancers, particularly in young women. Following a hysterectomy, the tissue is examined to see if the cancer has spread and requires additional radiation treatment. Women who have had hysterectomies cannot become pregnant, but complications from a hysterectomy are rare.

If cervical cancer recurs following treatment, a pelvic **exenteration** (extensive surgery) may be performed. This includes a radical hysterectomy, with the additional removal of the bladder, rectum, part of the colon, and/or all of the vagina. Such operations require the creation of new openings for the urine and feces. A new vagina may be created surgically. Often the clitoris and other outer genitals are left intact.

Recovery from a pelvic exenteration may take 6 months to 2 years. This treatment is successful with 40-50% of recurrent cervical cancers that are confined to the pelvis. If the recurrent cancer has spread to other organs, radiation or **chemotherapy** may be used to alleviate some of the symptoms.

Radiation

Radiation therapy, which involves the use of high-dosage x rays or other high-energy waves to kill cancer cells, often is used for treating stages IB, IIA, and IIB cervical cancers, or in combination with surgery. With external-beam radiation therapy, the rays are focused on the pelvic area from a source outside the body. With implant or internal radiation therapy, a pellet of radioactive material is placed internally, near the tumor. Alternatively, thin needles may be used to insert the radioactive material directly into the tumor.

Radiation therapy to the pelvic region can have many side effects:

- skin reaction in the area of treatment
- **fatigue**
- upset stomach and loose bowels
- vaginal stenosis (narrowing of the vagina due to build-up of scar tissue) leading to painful sexual intercourse
- premature menopause in young women
- problems with urination

Chemotherapy

Chemotherapy, the use of one or more drugs to kill cancer cells, is used to treat disease that has spread beyond the cervix. Most often it is used following surgery or radiation treatment. Stages IIB, III, IV, and recurrent cervical cancers usually are treated with a combination of external and internal radiation and chemotherapy. The common drugs used for cervical cancer are **cisplatin**, **ifosfamide**, and **fluorouracil**. These may be injected or taken by mouth. The National Cancer Institute recommends that chemotherapy with cisplatin be considered for all women receiving radiation therapy for cervical cancer.

The side effects of chemotherapy depend on a number of factors, including the type of drug, the dosage, and the length of the treatment. Side effects may include:

- **nausea and vomiting**
- fatigue
- changes in appetite
- hair loss (**alopecia**)
- mouth or vaginal sores
- infections
- menstrual cycle changes
- premature menopause
- infertility
- bleeding or **anemia** (low red blood cell count) With the exception of menopause and infertility, most of the side effects are temporary.

Alternative and complementary therapies

Biological therapy sometimes is used to treat cervical cancer, either alone or in combination with chemotherapy. Treatment with the immune-system protein interferon is used to boost the **immune response**. Biological therapy can cause temporary flu-like symptoms and other side effects.

Some research suggests that vitamin A (carotene) may help to prevent or stop cancerous changes in cells such as those on the surface of the cervix. Other studies suggest that **vitamins** C and E may reduce the risk of cervical cancer.

Prognosis

For cervical cancers that are diagnosed in the pre-invasive stage, the 5-year-survival rate is almost 100%. When cervical cancer is detected in the early invasive stages, approximately 91% of women survive 5 years or more. Stage IVB cervical cancer is not considered to be

curable. The 5-year-survival rate for all cervical cancers combined is about 70%. The death rate from cervical cancer continues to decline by about 2% each year. Women over age 65 account for 40-50% of all deaths from cervical cancer.

Coping with cancer treatment

Medications can ease some of the side effects of radiation and chemotherapy, such as nausea and menopausal symptoms. Premature menopause may require estrogen-replacement therapy, however in 2003, a large study called the Women's Health Initiative documented several health problems with hormone replacement therapy, so women should check with their physicians. Vaginal dilators and lubricants can relieve the effects of vaginal stenosis. A nutritious diet, rest, and a strong emotional support system help with recovery from treatment.

Following treatment for cervical cancer, additional tests are conducted to check for recurrence. These tests include frequent Pap smears, biopsies, and blood tests. X rays, CT or MRI scans, or other **imaging studies** such as ultrasound also may be used.

Clinical trials

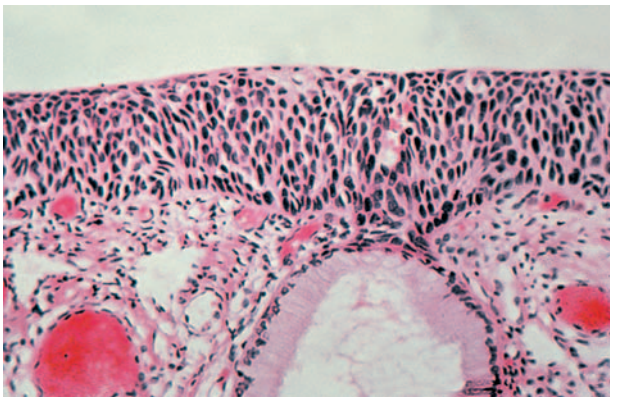
There are many **clinical trials**, ongoing throughout the United States, for the treatment of most stages of cervical cancer. These include the testing of new chemotherapy drugs, new methods of radiation therapy, and new combinations of surgery and radiation or chemotherapy. New methods for performing Pap tests also are being studied.

A new test for HPV, called the Hybrid Capture HPV test, is being studied. Results suggest that this test may be useful for determining which women with abnormal Pap test results should have colposcopy. Various types of HPV **vaccines** are being tested. These include vaccines that prevent HPV infection, vaccines for women infected with HPV, and vaccines for women with advanced cervical cancer. Scientists predict having FDA approval of an HPV vaccine by about 2008 or 2010.

Prevention

Viral infections

Most cervical cancers are preventable. More than 90% of women with cervical cancer are infected with HPV. HPV infection is the single most important risk factor. This is particularly true for young women because the cells lining the cervix do not fully mature until age 18. These immature cells are more susceptible to cancer-causing agents and viruses.



A biopsied section of the cervix indicating a carcinoma in situ. *(Custom Medical Stock Photo. Reproduced with permission.)*

Since HPV is a sexually transmitted infection, sexual behaviors can put women at risk for HPV infection and cervical cancer. These behaviors include:

- sexual intercourse at age 16 or younger
- partners who began having intercourse at a young age
- multiple sexual partners
- sexual partners who have had multiple partners (''high-risk males'')
- A partner who has had a previous sexual partner with cervical cancer HPV infection may not produce any symptoms, so sexual partners may not know that they are infected. However, Pap tests can detect the infection. Condoms do not necessarily prevent HPV infection. In 2003, a new DNA screening test was approved by the FDA to test for HPV at the same time as the Pap test. Condoms do not necessarily prevent HPV infection. However, in 2003, a preliminary study demonstrated that a vaccine against the type of HPV that causes the most cervical cancers showed promise in preventing HPV infection. Results were still preliminary.

Infection with the human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS) is a risk factor for cervical cancer. Women who test positive for HIV may have impaired immune systems that cannot correct precancerous conditions. Furthermore, sexual behavior that puts women at risk for HIV infection, also puts them at risk for HPV infection. There is some evidence suggesting that another sexually transmitted virus, the genital herpes virus, also may be involved in cervical cancer.

Smoking

Smoking may double the risk of cervical cancer. Chemicals produced by tobacco smoke can damage the

KEY TERMS

Adenocarcinoma—Cervical cancer that originates in the mucus-producing cells of the inner or endocervix.

Biopsy—Removal of a small sample of tissue for examination under a microscope; used for the diagnosis and treatment of cervical cancer and precancerous conditions.

Carcinoma in situ—Cancer that is confined to the cells in which it originated and has not spread to other tissues.

Cervical intraepithelial neoplasia (CIN)—Abnormal cell growth on the surface of the cervix.

Cervix—Narrow, lower end of the uterus forming the opening to the vagina.

Colposcopy—Diagnostic procedure using a hollow, lighted tube (colposcope) to look inside the cervix and uterus.

Conization—Cone biopsy; removal of a cone-shaped section of tissue from the cervix for diagnosis or treatment.

Dysplasia—Abnormal cellular changes that may become cancerous.

Endocervical curettage—Biopsy performed with a curette to scrape the mucous membrane of the cervical canal.

Human papilloma virus (HPV)—Virus that causes abnormal cell growth (warts or papillomas); some types can cause cervical cancer.

Hysterectomy—Removal of the uterus.

Interferon—Potent immune-defense protein produced by viral-infected cells; used as an anti-cancer and anti-viral drug.

Laparoscopy—Laparoscopic pelvic lymph node dissection; insertion of a tube through a very small surgical incision to remove lymph nodes.

Loop electrosurgical excision procedure (LEEP)—Cone biopsy performed with a wire that is heated by electrical current.

Lymph nodes—Small round glands, located throughout the body, that filter the lymphatic fluid; part of the body's immune defense.

Pap test—Pap smear; removal of cervical cells to screen for cancer.

Pelvic exenteration—Extensive surgery to remove the uterus, ovaries, pelvic lymph nodes, part or all of the vagina, and the bladder, rectum, and/or part of the colon.

Squamous cells—Thin, flat cells of the surfaces of the skin and cervix and linings of various organs.

Squamous intraepithelial lesion (SIL)—Abnormal growth of squamous cells on the surface of the cervix.

Vaginal stenosis—Narrowing of the vagina due to a build-up of scar tissue.

DNA of cervical cells. The risk increases with the number of years a woman smokes and the amount she smokes. A 2003 study also linked smoking to poorer outcomes and survivals in cervical cancer patients.

Diet and drugs

Diets that are low in fruits and vegetables increase the risk of cervical cancer. A 2003 study also linked obesity to increased risk for cervical adenocarcinoma. Even women who were overweight had a higher incidence of the disease. The link appears to be increase levels of estrogen. Excessive fat tissue influences levels of estrogen and other sex hormones. Women also have an increased risk of cervical cancer if their mothers took the drug diethylstilbestrol (DES) while they were pregnant. This drug was given to women between 1940 and 1971 to prevent miscarriages. Some statistical studies have suggested that the long-term use of oral contraceptives may slightly increase the risk of cervical cancer.

Pap tests

Most cases of cervical cancers are preventable, since they start with easily detectable precancerous changes. Therefore, the best prevention for cervical cancer is a regular Pap test. The ACS revised its guidelines for regular screening in late 2002. In brief, women should begin having Pap tests about three years after having sexual intercourse, but no later than 21 years of age. Women should continue screening every year with regular Pap tests until age 30. Once a woman has had three normal results in a row, she may get screened every two to three years. A doctor may suggest more frequent screening if a woman has certain risk factors for cervical cancer. Women who have had total hysterectomies including the removal of the cervix and those over age 70 who have had three normal results generally do not need to continue having Pap tests under the new guidelines.

The National Breast and Cervical Cancer Early Detection Program provides free or low-cost Pap tests and

treatment for women without health insurance, for older women, and for members of racial and ethnic minorities. The program is administered through individual states, under the direction of the Centers for Disease Control and Prevention.

Special concerns

If a woman is diagnosed with very early-stage (IA) cervical cancer while pregnant, the physician usually will recommend a hysterectomy after the baby is born. For later-stage cancers, the **pregnancy** is terminated or the baby is removed by **cesarean section** as soon as it can survive outside the womb. This is followed by a hysterectomy and/or radiation treatment. For the most advanced stages of cervical cancer, treatment is initiated despite the pregnancy.

Many women with cervical cancer have hysterectomies, which are major surgeries. Although normal activities, including sexual intercourse, can be resumed in 4-8 weeks, a woman may have emotional problems following a hysterectomy. A strong support system can help with these difficulties.

See also Gynecologic cancers.

QUESTIONS TO ASK THE DOCTOR

- What type of biopsy will I have? What type of anesthetic will be used? What are the after-effects?
- What type of cervical cancer do I have?
- What is the stage of my cancer?
- What are my treatment choices?
- Which treatment do you recommend and why?
- What should I do to prepare for treatment?
- What are the side effects of this treatment and how can I alleviate them?
- What is the recovery period for this treatment?
- Will I be able to get pregnant after this treatment?
- Are there clinical trials that may be appropriate for me?
- What is my prognosis?

Resources

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Road, N.E., Atlanta, GA 30329. (800) ACS-2345. <http://www.cancer.org>. Information, funds for cancer research, prevention programs, and patient services, including educational and support programs for patients and families and temporary accommodations for patients.

Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. Mail Stop K-64. 4770 Buford Highway NE, Atlanta, GA 30341-3717. (770) 488-4751. (888) 842-6355. <http://www.cdc.gov/cancer>. Research and public education and outreach for disease prevention under the U.S. Department of Health and Human Services.

EyesOnThePrize.Org. 446 S. Anaheim Hills Road, #108, Anaheim Hills, CA 92807. <http://www.eyesontheprize.org>. On-line information and emotional support for women with gynecologic cancer.

Gynecologic Cancer Foundation. 401 North Michigan Avenue, Chicago, IL 60611. (800) 444-4441. (312) 644-6610. <http://www.wcn.org/gcf/>. Research, education, and philanthropy for women with gynecologic cancer.

National Cancer Institute. Public Inquiries Office, Building 31, Room 10A31, 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (800)-4-CANCER. <http://www.nci.nih.gov/>. <http://cancernet.nci.nih.gov>. Research, information, and clinical trials.

National Cervical Cancer Coalition. 16501 Sherman Way, Suite #110, Van Nuys, CA 91406. (800) 685-5531. (818) 909-3849. <http://www.nccc-online.org/>. Information, education, access to screening and treatment, and support services; sponsors the Cervical Cancer Quilt Project.

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Chemoembolization

Definition

Utilized to treat tumors in the liver, chemoembolization is the process of injecting **chemotherapy** directly into the blood vessels which feed the tumor.

Purpose

Chemoembolization is a treatment that can be focused on cancerous cells that have spread to the liver but does not expose the rest of the body to the effects of chemotherapy. It is not a cure but does offer relief (palliative) and preserves the quality of life. The technique is minimally invasive and approximately 70% of patients will experience improvement in liver function and survival time.

Precautions

The referring physician will probably recommend several tests prior to the procedure, such as, liver function blood tests and a CAT scan or an MRI of the liver. These tests insure there is no blockage of the portal vein in the liver; there is no cirrhosis of the liver; and there is no blockage of the bile ducts. Any of these complications may prevent the procedure from being performed.

Description

A radiologist performs this procedure in a hospital under x-ray guidance by inserting a small catheter (tiny tube) through a hollow needle into the femoral artery, located in the groin. It is then threaded up through the aorta and into the artery in the liver that feeds the tumor. During chemoemolization, three chemotherapy drugs are injected directly into this artery and it is then "embolized" or blocked off with a mixture of oil and tiny particles. Since the drugs are injected directly into the tumor, the dosage is 20-200 times greater than that received with standard treatment via a vein in the arm. Since the tumor is blocked off, the drugs stay in it for a much longer time. Also, with the blood supply blocked, the tumor is deprived of oxygen and nutrients, which serves to hasten its destruction. The liver has two blood supplies, a hepatic artery and a large portal vein so it can still function with one blocked off.

The procedure takes approximately three hours to perform, occurs while the patient is under conscious sedation, and usually involves an overnight stay in the hospital. It is usually performed on a monthly basis with three sessions being the average treatment regimen.

Preparation

The evening before the procedure nothing may be taken by mouth after dinner. Generally, a patient must arrive at the hospital early in the morning to permit the infusion of large amounts of fluids by an intravenous (IV) line placed in the arm. These fluids contain **antibiotics** and other medications needed prior to the procedure. The patient is then taken to the Department of Radiology for the treatment.

Aftercare

Immediately following the injection of the chemotherapy mixture, the patient is returned to a hospital room and must lie flat in bed for at least six hours. More IV fluids are provided during this time as well as overnight. Most patients are discharged the next day. It is

KEY TERMS

CAT—Computerized axial tomography, also called computed tomography.

Chemotherapy—The treatment of illness by chemical means, by medications.

Liver function tests—Laboratory procedures that measure some aspect of liver functions and involves a wide range of tests.

MRI—Magnetic resonance imaging

cirrhosis—A liver disease characterized by the loss of normal microscopic structures within the liver that are replaced by fibrous tissue that cause the organ to constrict and divide into irregular nodules.

Palliative—Any treatment that offers relief but does not cure.

important to spend as much time as possible in bed 1-2 days following the procedure in order to improve blood flow to the liver.

Risks

Serious complications are extremely rare from this procedure. Some statistics have quoted that in less than 3% of the procedures, the liver tumor that was destroyed became infected and abscessed. Others have noted approximately one fatality per 100 procedures due to liver failure.

Normal results

The patient may experience varying degrees of pain, **fever** and nausea following the treatment, which may last any where from a few hours to a few days. Pain or high fevers the first few days following the treatment are a result of the tumor breaking down and is normal. Frequently, a medication (a laxative) called Lactulose is given to help the body rid itself of metabolic waste usually eliminated by the liver. This may cause loose stools for several days. Extreme **fatigue** is a common problem for three to four weeks after the procedure. With the tumor now blocked, liver function should improve and thus, the quality of life.

Follow-up scans may be performed in order to determine any changes in the tumor and to look for the appearance of any new tumors. Chemoembolization can be repeated many times over a period of many years depending on the status of the patient.

QUESTIONS TO ASK THE DOCTOR

- Am I a good candidate for this procedure?
- Do I have any contraindications that should be considered before having the procedure?
- Will I experience any improvement in my quality of life?
- What are the advantages and disadvantages of the procedure?
- Does the physician performing the procedure do this often or just once in awhile?

Abnormal results

A sudden change in the degree of pain and/or fever that persists after the first week should be reported to a physician. Any unusual changes should be communicated immediately.

Resources

BOOKS

American Cancer Society's Consumer's Guide to Cancer Drugs. Jones and Bartlett, 2000.

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American Cancer Society. P.O. Box 102454, Atlanta, GA 30368-2454. <http://www.ca.cancer.org>.

American Society of Clinical Oncology,1900 Duke Street, Suite 200, Alexandria, VA 22314. Phone: 703-299-0150. <http://www.asco.org>.

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Chemoprevention

Definition

Chemoprevention is the attempt to prevent cancer from developing by using substances that interfere in the process of **carcinogenesis**.

Purpose

Clinical trials are currently investigating chemoprevention for people at high risk of certain cancers. For instance, to prevent **breast cancer** in the second breast of women who have already been treated for breast cancer, or women who have never had breast cancer but are determined to be at high risk; or to prevent **colon cancer** in people with a genetic predisposition for the cancer. Individuals not at a particularly high risk can use behavioral and dietary modifications for chemoprevention. Since the 1980s, the National Cancer Institute has identified more than 1,000 natural and synthetic chemicals with some degree of cancer preventive activity. Currently, more than 400 potential agents are under investigation for their ability to prevent cancer and at least 40 compounds or combinations are undergoing human clinical trials.

Chemopreventive agents have been identified that interact with all stages of carcinogenesis: initiation, promotion and progression. They work by inactivating carcinogens (cancer-causing agents), inducing enzymes, or as **antioxidants**. Later in the process they may inhibit tumor growth by acting as suppressors or stimulating apoptosis.

Description

Chemoprevention differs from **chemotherapy** in that it is used long before cancer develops to prevent cancer or to inhibit pre-cancer, possibly in at-risk individuals. Chemotherapy, on the other hand, seeks to kill cells that already have become cancerous. Chemoprevention uses natural products from foods or synthetic preparations. Because chemoprevention is used long term, it must be non-toxic, effective, easy to administer, and inexpensive. Few specific agents are currently advised for widespread clinical use since clinical trials that last up to 15 years are still ongoing.

Strategies for chemoprevention change often based on clinical trial results and scientific discoveries. For example, scientists completed the first map of the human genome (genetic makeup) in mid-2002. Since that time, cancer research has evolved rapidly. Epigenetic events, or the alterations in gene expressions without certain DNA involvement, may lead to cancer chemopreventive drug development aimed at tumor suppressor genes.

Dietary factors and lifestyle changes are important areas in chemoprevention. It is estimated that through dietary improvements there could be a 50% reduction in colon and rectal cancers, a 25% reduction in breast cancer and a 15% reductions each in prostate, endometrial and gallbladder cancers. Cancers of the stomach, esophagus, pancreas, ovaries, liver, lung, and bladder also may be affected by dietary factors. However, these improvements probably should come from the diet rather than from dietary supplements. In 2003, the U.S. Preventive Services Task Force released a report stating that evidence was insufficient to recommend for or against use of vitamin supplements to help prevent cancer. The task force recommended against supplementation with beta carotene because of higher incidence of lung cancer among those who used certain levels of beta carotene supplements.

Phytochemicals from food are a source of many chemopreventive agents. Garlic alone contains 30 cancer preventing compounds including selenium. Broccoli contains indole-3-carbinol as well as phenethylisothiocyanate, a sulfur-containing compound. Soy products contain phytoestrogens such as genistein. Tea, both black and green, contains an abundance of polyphenols such as the catechins that have antioxidant and anti-cancer activity. Compounds in tea also have antiestrogen activity and can modulate detoxification enzymes. Curcumin from the spice turmeric is gaining attention as a chemopreventive agent. It is both an anti-inflammatory agent and an antioxidant. In laboratory animals curcumin has shown inhibition toward colon, breast, and **stomach cancer**.

Chemoprevention of breast cancer

Antiestrogens can counteract the growth effect estrogen has on some breast cancers. Two **antiestrogens**, **tamoxifen** and **raloxifene**, have been shown in clinical trials to prevent breast cancer in women at high risk for the disease. As a result of these trials, tamoxifen has been approved by the FDA as a preventive therapy as well as a treatment. Other antiestrogens, including soy isoflavones, are still under investigation. The synthetic retinoid, fenretinide, also shows promise in preventing breast cancer. Also under investigation are indole-3-carbinol from broccoli.

Chemoprevention of colon cancer

Because there are more identifiable **tumor markers** known for colon cancer, the evaluation of chemopreventive agents can be a shorter process. The recurrence of polyps rather than the development of malignant cancer can be used as an endpoint. Inflammation has been linked to cancer for some time and the anti-inflammatory agents sulindac and sulindac sulfone as well as specific **cyclooxygenase-2 inhibitors** are proving useful in preventing colon cancer. Adding fruits and vegetables to the diet also appears from epidemiological studies to have a protective effect on colon cancer.

Chemoprevention of prostate cancer

Antiandrogens and antiestrogens are both important in preventing **prostate cancer**. Finasteride is under investigation as an anti-estrogen to prevent prostate cancer in at-risk men. Finasteride is a drug that can reduce the levels of dihydrotestosterone, which is associated with prostate enlargement and possibly cancer. It has been used to treat enlarged prostate and is currently being investigated to prevent prostate cancer in men over the age of 55 years. Men at an increased risk for prostate cancer include those with a history of prostate cancer, those with a high-fat diet, increasing age, and those of African-American descent. Soy products and indole-3-carbinol may also be effective for this reason. Lycopene, a vitamin A-like compound found in tomatoes and other red fruits and vegetables is associated with a decreased risk of prostate cancer. Both selenium and tea may also have chemopreventive effects on prostate cancer.

Chemoprevention of skin cancer

The incidence of skin cancer has dramatically increased in recent years, probably due to the popularity of sun tanning. Compounds under investigation for the prevention of skin cancer include compounds from tea, silymarin from milk thistle, vitamin A and coumarins found in a number of plants.

Recommendations

Changes in lifestyle can significantly affect an individual's risk for cancer. It is estimated that 32% of colon cancers are related to physical inactivity, which may also play a part in other cancers. Tobacco accounts for 30% of all cancers, not just lung cancer. **Alcohol consumption** is related to cancers of the oral cavity, pharynx, larynx, esophagus, and liver, and possibly colorectal and breast cancers. The combination of alcohol and tobacco is especially dangerous. The main cause of skin cancers is exposure to UV radiation. Fair skinned individuals are at an increased risk. Obesity puts an individual at an increased risk of death from uterus, gallbladder, kidney, stomach, colon, breast, and prostate cancers.

The lifestyle recommendations from the American Cancer Society for preventing cancer include:

- Maintain a desirable body weight.
- Eat a variety of foods.
- Include both fruits and vegetables in the daily diet.
- Eat more high-fiber foods.
- Cut down on total fat intake.
- Limit consumption of alcoholic beverages.

KEY TERMS

apoptosis—A process of cell death performed by a damaged cell.

anti-inflammatory—An agent that reduces inflammation. The most common example is aspirin.

phytochemical—A non-nutrient compound from plants.

- Limit consumption of salt-cured, smoked and nitrite preserved foods.

Risks

Because chemopreventive agents can be administered in high doses and for long periods of time, the risk of side effects is increased. During the 1980s, the CARET study found that beta-carotene actually increased the risk of lung cancer in male smokers. Studies of tamoxifen to prevent breast cancer show the drug can increase the risks of uterine cancer, and cause other serious side effects. Long-term use of non-steroidal anti-inflammatory drugs to prevent colon cancer can result in gastrointestinal problems and liver toxicity. Current recommendations are to increase consumption of fruits, vegetables and fiber in the diet rather than taking supplements.

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Chemotherapy

Definition

Chemotherapy is the systemic (whole body) treatment of cancer with anticancer drugs.

Purpose

The main purpose of chemotherapy is to kill cancer cells. It can be used as the primary form of treatment or as a supplement to other treatments. Chemotherapy is often used to treat patients with cancer that has spread from the place in the body where it started (metastasized), but it may also be used the keep cancer from coming back (adjuvant therapy). Chemotherapy destroys cancer cells anywhere in the body. It even kills cells that have broken off from the main tumor and traveled through the blood or lymph systems to other parts of the body.

Chemotherapy can cure some types of cancer. In some cases, it is used to slow the growth of cancer cells or to keep the cancer from spreading to other parts of the body. When a cancer has been removed by surgery, chemotherapy may be used to keep the cancer from coming back (adjuvant therapy). It is also helpful in reducing the tumor size prior to surgery (primary [neoadjuvant] chemotherapy). Chemotherapy can ease the symptoms of cancer (palliate), helping some patients have a better quality of life.

Types of chemotherapy

Chemotherapy may be used as the first line of treatment or it may be started after a tumor is removed. A variety of factors, including the type and stage of cancer, will determine the type of chemotherapy used.

Adjuvant chemotherapy

Adjuvant chemotherapy refers to giving patients anticancer drugs after the primary tumor has been removed and there is no evidence that cancer remains in the body. It was first studied in the 1950s. This form of treatment initially gained popularity because it showed promise in improving the survival for patients with certain cancers. The theory was that adjuvant chemotherapy would attack microscopic cancer cells that remained after tumor removal. Adjuvant chemotherapy may be effective in some types of cancers, including **breast cancer**, colorectal cancer, osteogenic sarcoma, and **Wilms' tumor**.

A patient's response to adjuvant therapy is determined by a variety of factors, including drug dosage, schedule of drug therapy, and **drug resistance**. Toxic side effects and cost-effectiveness are other important issues. This area is undergoing further investigation.

Primary (neoadjuvant) chemotherapy

Primary chemotherapy, also sometimes called neoadjuvant chemotherapy or induction chemotherapy, is the use of anticancer drugs as the main form of treatment. Chemotherapy can be the primary treatment with cancers such as these: certain lymphomas, childhood and some adult forms of **Hodgkin's disease**, Wilms' tumor, embryonal **rhabdomyosarcoma**, and small cell lung cancer.

Primary chemotherapy can also be used to treat tumors prior to surgery or radiation. In some cases, the tumor may be so large that surgery to remove it would destroy major organs or would be quite disfiguring. Primary neoadjuvant chemotherapy may reduce the tumor size, making it possible for a surgeon to perform a less traumatic operation. Examples of cancers in which primary chemotherapy may be followed-up with less extensive surgeries include: **anal cancer**, **bladder cancer**, breast cancer, **esophageal cancer**, **laryngeal cancer**, osteogenic sarcoma, and soft tissue sarcoma.

An advantage of primary chemotherapy is that the blood vessels are intact since they have not been exposed to surgery or radiation. Therefore, drugs can easily travel through the bloodstream toward the tumor. In fact, the therapy can improve the tumor's blood flow, making it more receptive to the impact of radiation. In addition, the use of chemotherapy before surgical removal of cancer allows the physician to assess the responsiveness of the tumor to the drug(s) used. Since not all chemotherapy regimens are equally effective, knowing how a particular tumor responds to the chemotherapy regimen prescribed can be an advantage in treating the disease.

Primary chemotherapy does have drawbacks. Some cancer cells may be drug-resistant, making the therapy ineffective. (Although discovering that the drug is ineffective minimizes the number of cycles of the drug that the patient must undergo.) The drug may not significantly reduce tumor size, or the tumor may continue to grow despite treatment. Furthermore, the initial use of a drug may lead to higher toxicity when chemotherapy is given later in the course of treatment.

Primary chemotherapy is becoming the norm in treating some patients with certain cancers, such as specific types of lymphomas, some small cell lung cancers, **childhood cancers**, **head and neck cancers**, and locally advanced breast cancer. Additional research using this type of chemotherapy is underway.

Combination chemotherapy

In most cases, single anticancer drugs cannot cure cancer alone. The use of two or more drugs together is often a more effective alternative. This approach is called combination chemotherapy. Scientific studies of different drug combinations help doctors learn which combinations work best for various types of cancers.

Combination chemotherapy provides a higher chance of destroying cancerous cells. An oncologist decides which chemotherapy drug or combination of drugs will work best for each patient. Different drugs attack cancer cells at varying stages of their growth cycles, making the combination a stronger weapon against cancerous cells. Furthermore, using a combination of drugs may reduce the chance of drug resistance.

When selecting the combination of drugs, a variety of factors are examined. It is important for each drug to be effective against the particular tumor being targeted. Toxicity must also be studied to be sure that each different drug used in a combination is not toxic for the same organ. For example, if two drugs are each toxic to the liver, the combination could be more damaging to that organ.

How chemotherapy is given

Chemotherapy medications enter a person's body in different ways, depending on the drugs to be given and the type of cancer.

The goal is for the chemotherapy drug to reach the tumor. Some areas of the body are less accessible for anticancer drugs, and this is considered when the doctor determines the route of administration. For example, the blood-brain barrier refers to the inability of some anticancer drugs to travel through the bloodstream and enter the brain or the fluid surround the brain. Areas of the body that are inaccessible to a particular drug create a phenomenon called the sanctuary effect. In other words, the tumor is safe because the chemotherapy cannot reach it. To overcome a problem such as this one, the doctor must consider the route that will most effectively deliver the drug to the cancerous cells. Chemotherapy may be given by one or more of the following methods:

- oral (by mouth)
- injection (intramuscular or subcutaneous)
- intravenous (IV)
- intra-arterial (into the arteries)
- intralesional (directly into the tumor)
- intraperitoneal (into the peritoneal cavity)
- intrathecal (into the spinal fluid)
- topically (applied to the skin)

Types of chemotherapy

Type	Definition
Adjuvant	Given to improve survival when cancer is no longer evident
Primary (formerly called neo-adjuvant)	Use of chemotherapy drugs as main treatment, or as a treatment prior to surgery or radiation
Induction	Initiation of chemotherapy with plans for further treatments
Combination	Use of two or more chemotherapy drugs together

Orally

Oral chemotherapy is given by mouth in the form a pill, capsule, or liquid. This is the easiest method and can usually be done at home.

Injection

Intramuscular (IM) chemotherapy is injected into a muscle. Chemotherapy given by intramuscular injection is absorbed into the blood more slowly than IV chemotherapy. Because of this, the effects of IM chemotherapy may last longer than chemotherapy given intravenously. Chemotherapy may also be injected subcutaneously (SQ or SC), which means under the skin.

Intravenous

Intravenous (IV) chemotherapy is the most common way to deliver anticancer drugs into a person's body. The drug is injected directly into a vein. A small needle is inserted into a vein on the hand or lower arm.

Chemotherapy may also be given by a catheter or port inserted into a central vein or body cavity, where it can

remain for an extended period of time. A port is a small reservoir or container that is placed in a vein or under the skin in the area where the drug will be given. These methods eliminate the need for repeated injections and may allow patients to spend less time in the hospital while receiving chemotherapy. A common location for a permanent catheter is the external jugular vein in the neck. Catheters and ports require meticulous care and cleaning to avoid complications, such as blood clots or infection. They may be inserted using a surgical procedure.

Chemotherapy given by the IV method may be administered intermittently or continuously. The main reasons for a continuous flow are to increase effectiveness against the tumor or to lower toxicity. Some drugs perform more effectively when exposed to the cancer over a period of time, making a continuous flow more desirable. A drug that is commonly used to treat colorectal cancer in continuous infusions is 5-fluorouracil, also known as 5-FU or **fluorouracil**. A drug that has less toxicity to the heart with continued infusion is **doxorubicin**, also known as Adriamycin. In some cases, toxicity occurs when the drug reaches a peak level. Offering a continuous infusion prevents the drug from reaching this level, thus lowering the chance of toxic side effects.

Intra-arterial

Cancerous tumors require a supply of blood and oxygen so that they can grow. They get these essentials from the arteries that supply organs with their blood and oxygen. Putting chemotherapy drugs into the arteries provides good access to the cancerous tumor. Intra-arterial chemotherapy is not designed for all patients. The tumor must be confined to one specific organ and the blood supply to the tumor must be accessible. The liver is the most common organ targeted in this type of chemotherapy, although it is also effective in certain brain cancers. Its use in head and neck cancers remains controversial. Further use of this type of chemotherapy is being investigated.

A catheter is inserted using radiologic techniques or surgery. Surgical insertion is the most common. Although it is less costly and less stressful, radiologic insertion results in a catheter that cannot stay in place as long as one inserted surgically. A radiologically inserted catheter stays in place for weeks compared to surgically inserted catheters designed to stay in place from weeks to years. In the long run, the surgically implanted arterial catheter has fewer complications, such as thrombosis or infection, and is more highly acceptable to the patient.

The radiologically placed catheter is initially inserted into an artery in the person's arm or leg, and then it is guided to its final destination near the tumor, where it can remain for an extended period.

Chemotherapy

Routes of delivering chemotherapy	Some common drugs used
Oral	Capecitabine
Intravenous	Fluorouracil (5–FU) Doxorubicin
Intra-arterial (into the arteries)	Floxuridine Fluorouracil BUDR FCNU Doxorubicin Mitomycin-C Cisplatin Streptomycin
Intralesional (directly into the tumor)	Vinblastine Vincristine
Intraperitoneal (into the cavity surrounding the abdominal organs)	Cisplatin Paclitaxel Floxuridine Fluorouracil Mitoxantrone Carboplatin Alpha interferon
Intrathecal (into the spinal fluid)	Methotrexate Cytarabine
Topical (applied to skin)	Fluorouracil

The catheters require meticulous care to keep them clean and securely in place, which lessen the chance of complications. Problems associated with catheters include movement of the tip, blood clots and infection.

Pumps may be used to move the drug through the artery and into the tumor. A pump may be external or internally planted. External pumps range from large machines found in hospitals to portable wallet-sized devices. Implanted pumps give patients greater freedom, and are safe and effective. Some internal pumps deliver a constant flow of drugs, while others are programmed to deliver intermittent doses.

Drugs used for intra-arterial chemotherapy include FUDR (**floxuridine**), fluorouracil, mitomycin, **cisplatin**, and streptomycin. Less frequently, doxorubicin has been used intra-arterially for treating certain cancers of the breast, bladder, stomach, and other areas.

Intralesional

Intralesional chemotherapy is the injection of anticancer drugs directly into a tumor that is in the skin, under the skin, or in an organ inside the body. Some examples involving the use of intralesional chemotherapy include **melanoma** and **Kaposi's sarcoma**. This type of chemotherapy shows promise for other malignancies such as laryngeal cancers, and further uses are under investigation.

Intraperitoneal

Intraperitoneal (IP) chemotherapy is administered into the abdominal cavity through a catheter or port that is put into place by surgery.

Ovarian cancer is sometimes treated with IP chemotherapy because this type of cancer usually stays within a confined area. This type of therapy is only suitable for some patients. Ovarian cancer patients whose tumors

have a diameter greater than two centimeters may not receive this therapy because the anticancer drug does not reach very far into the tumor. Also, patients whose cancers are resistant to certain drugs may not undergo IP therapy. Patients with smaller tumors, or those who show response to chemotherapy are better candidates.

Drugs used in IP chemotherapy include cisplatin, **paclitaxel**, floxuridine, 5-FU, **mitoxantrone**, **carboplatin**, and alfa-interferon.

Intrathecal

Intrathecal chemotherapy is the injection of anticancer drugs into the spinal fluid. This method is used primarily in treating **acute lymphocytic leukemia**. It is effective in placing the anticancer drug directly into the cerebrospinal fluid that surrounds the spinal cord and the brain. A spinal tap, also called **lumbar puncture**, is the procedure usually used to gain access to the spinal fluid. If many treatments are needed, a device called an **Ommaya reservoir** may be used. This device is inserted under the scalp and allows injection of anticancer drugs throughout the spinal fluid via the reservoir. Patients can go home with the Ommaya reservoir in place. Common drugs used intrathecally include **methotrexate** and **cytarabine**, which are usually given by a doctor with a nurse's assistance. Some leukemia patients receive IV treatments at the same time they are having intrathecal treatments.

Topical chemotherapy

Topical chemotherapy is given as a cream or ointment applied directly to the cancer. This method is more common in the treatment of certain types of skin cancer. An example is fluorouracil, also known as 5-FU, which is a topical anticancer cream.

Chemotherapy drugs

More than 50 chemotherapy drugs are currently available to treat cancer and many more are being tested for their ability to destroy cancer cells. About 30% of anticancer drugs come from or are derived from natural sources. Most chemotherapy drugs interfere with the cell's ability to grow or multiply. Although these drugs affect all cells in the body, many useful treatments are most effective against rapidly growing cells. Cancer cells grow more quickly than most other body cells. Other cells that grow fast are cells of the bone marrow that produce blood cells, cells in the stomach and intestines, and cells of the hair follicles. Therefore, the most common side effects of chemotherapy are linked to their effects on other fast growing cells. Some tumor cells are resistant to drugs, making them more difficult to target.

Alkylating agents

Alkylating drugs kill cancer cells by directly attacking DNA, the genetic material of the genes. By attacking the DNA, the drug prevents the cell from forming new cells. Nitrogen mustards, which were the first nonhormonal chemicals with anticancer abilities, are alkylating drugs. **Cyclophosphamide** and Mustargen are two alkylating agents. Cyclophosphamide, the most common alkylating agent, is often used in combination with other drugs to treat breast cancer, lymphomas, and other tumors in both children and adults. Mustargen is part of the treatment for Hodgkin's disease.

Platinum drugs

Drugs containing platinum are useful in treating a number of malignant tumors. Examples of these drugs include cisplatin, carboplatin, and **oxaliplatin**. Cisplatin is more toxic than the other two, and it is subject to resistance by the cancerous tumors. In fact, it was cisplatin's high toxicity that prompted the discovery of the other two platinum drugs, which are less toxic and more effective. Carboplatin has been shown to cause less **nausea and vomiting** than cisplatin, and it has replaced cisplatin in many treatment regimes. New platinum drugs are being investigated.

Antimetabolites

Antimetabolites interfere with the production of DNA and keep cells from growing and multiplying. They are used to treat a variety of cancers including breast cancer, leukemia, **lymphoma**, colorectal cancer, head and neck cancer, osteogenic sarcoma, choriocarcinoma (a rare uterine cancer), and urothelial cancer. Some drug resistance has occurred with these types of drugs. Examples of antimetabolites are 5-fluorouracil (5-FU), Tegafur, and Uracil.

Antitumor antibiotics

Antitumor **antibiotics** are made from natural substances such as fungi in the soil. They interfere with important cell functions, including production of DNA and cell proteins. Doxorubicin, **daunorubicin**, **idarubicin**, **epirubicin**, **dactinomycin**, and **bleomycin** belong to this group of chemotherapy drugs.

Topoisomerase inhibitors

Topoisomerase inhibitors are effective in treating a number of cancers. Topoisomerase is an enzyme necessary for the replication of DNA within the cell. The topoisomerase inhibitors act on this enzyme, and the cell eventually dies. Drugs in this class include **etoposide** and **teniposide**.

Camptothecin analogues are also classed as topoisomerase inhibitors. Specific drugs are **topotecan** and **irinotecan**.

Anthracyclines are topoisomerase inhibitors such as daunorubicin, doxorubicin, epirubicin, and idarubicin. A drawback of the anthracyclines is their toxicity to the heart. Because of this, there have been efforts to develop synthetic drugs similar to the anthracyclines. Mitoxantrone and losoxantrone are two examples of synthetics.

Dactinomycin is another drug acting on the DNA of the cell. It is an effective drug for treating a variety of cancers including **Ewing's sarcoma**, Wilms' tumor, embryonal rhabdomyosarcoma, and gestational choriocarcinoma (rare uterine cancer). It has also been used to treat cancer of the testicles, lymphoma, and Kaposi's sarcoma.

Antimicrotubule Agents

A microtubule is an important part of a cell, and is the target of a class of anticancer drugs.

Vinca alkaloids, which attack the cell's microtubules, are found in very small amounts in the periwinkle plant. Three types of vinca alkaloids are **vincristine**, **vinblastine** and **vinorelbine**. Vincristine is used more frequently in treating childhood, rather than adult, cancers. It is used in combination chemotherapy for the treatment of acute lymphocytic leukemia and Hodgkin's and non-Hodgkin's lymphoma, as well as other cancers. Vinblastine is used in combination chemotherapy for Kaposi's sarcoma, as well as cancers of the bladder, brain and breast. It is also used in the treatment of advanced cases of lymphoma and germ cell cancers.

The taxanes are another group of antimicrotubule agents. They are from the Pacific yew tree, and were first isolated in 1963. In 1971, **paclitaxel** was found to be an active ingredient in the bark of this tree. Paclitaxel has shown promising results in people with cancers of the ovaries or breasts. It is also used for AIDS patients who have Kaposi's sarcoma, and in combination with cisplatin in the treatment of non-small cell lung cancer. Paclitaxel is also part of the chemotherapy treatment in breast cancer patients whose cancer has spread to the lymph nodes. A related drug, **docetaxel** is used for treating advanced cases of breast cancer as well as certain non-small cell lung cancers.

Estramustine phosphate is related to nitrogen mustard. This drug acts on the microtubule of the cell, and has been effective in treating certain prostate cancers.

Hormones

Steroid hormones slow the growth of some cancers that depend on hormones. For example, **tamoxifen** is used to treat breast cancers that depend on the hormone estrogen for growth. Additionally, androgen suppression therapy is used in the treatment of **prostate cancer**. The goal of this therapy is to lower the levels of male hormones (androgens), especially **testosterone**, that can cause prostate cancer cells to grow. Lutenizing hormone-releasing hormone (LHRH) analogs lower testosterone levels by decreasing the androgens produced by the testicles. Two LHRH analogs available in the U.S. in 2001 are **leuprolide acetate** and **goserelin**.

Treatment location and schedule

Patients may take chemotherapy at home, in the doctor's office, or as an inpatient or outpatient at the hospital. Most patients stay in the hospital when first beginning chemotherapy, so their doctor can check for any side effects and change the dose if needed. A very important part of chemotherapy is determining the appropriate dose. To do this, the doctor must consider the person's size as well as any toxic side effects the drug may have.

How often and how long chemotherapy is given depends on the type of cancer, how patients respond to the drugs, patients' health and ability to tolerate the drugs, and on the types of drugs given. Chemotherapy administration may take only a few minutes or may last as long as several hours. Chemotherapy may be given daily, weekly, or monthly. A rest period may follow a course of treatment before the next course begins. In combination chemotherapy, more than one drug may be given at a time, or they may be given alternately, one following the other.

Precautions

There are many different types of chemotherapy drugs. Oncologists, doctors who specialize in treating cancer, determine which drugs are best suited for each patient. This decision is based on the type of cancer, the patient's age and health, and other drugs the patient is taking. Some patients should not be treated with certain chemotherapy drugs. Age and other conditions may affect the drugs with which a person may be treated. Heart disease, kidney disease, and diabetes are conditions that may limit the choice of treatment drugs. Pregnancy is another precaution because of the anticancer drug's impact on fetal development.

Preparation

A number of medical tests are done before chemotherapy is started. The oncologist will determine how much the cancer has spread from the results of x rays and other imaging tests and from samples of the tumor taken during surgery.

A patient's complete medical history will be taken, including any past chemotherapy. The patient will be asked to sign a consent form, and will be told about the drugs and procedures involved with chemotherapy. It is essential that the patient understand both the risks and benefits of treatment.

The nurse explains what will take place during the treatment, and what side effects to expect. In addition to the physical side effects, the stress of chemotherapy will be discussed. Patients who are better prepared tend to have fewer side effects and a higher emotional ability to handle the chemotherapy treatments.

Blood tests give the doctor important information about the function of the blood cells and levels of chemicals in the blood. A complete blood count (CBC) is commonly done before and regularly during treatment. The CBC shows the numbers of white blood cells, red blood cells, and platelets in the blood. Because chemotherapy affects the bone marrow, where blood cells are made, levels of these cells often drop during chemotherapy. The white blood cells and platelets are most likely to be affected by chemotherapy. A drop in the white blood cell count means that the immune system cannot function properly. Low levels of platelets can cause a patient to bleed easily from a cut or other wound. A low red blood cell count can lead to **anemia** (deficiency of red blood cells) and **fatigue**.

When a chemotherapy treatment takes a long time, the patient may prepare for it by wearing comfortable clothes. Bringing a book to read or a tape to listen to may help pass the time and ease the stress of receiving chemotherapy. Some patients bring a friend or family member to provide company and support during treatment.

Sometimes, patients taking chemotherapy drugs known to cause nausea are given medications called **antiemetics** before chemotherapy is administered. Antiemetic drugs help to lessen feelings of nausea. Two antinausea medications that may be used are Kytril and Zofran.

Other ways to prepare for chemotherapy and help lessen nausea are:

- Regularly eat nutritious foods and drink lots of fluids.
- Eat and drink normally until about two hours before chemotherapy.
- Eat high carbohydrate, low-fat foods and avoid spicy foods.

Aftercare

To control side effects after chemotherapy, patients should:

- Follow any instructions given by the doctor or nurse.
- Take all prescribed medications.
- Eat small amounts of bland foods.
- Drink lots of fluids.
- Get plenty of rest.

Some patients find it helps to breathe fresh air or get mild exercise, such as taking a walk.

Risks

Chemotherapy drugs are toxic to normal cells as well as cancer cells. A dose that will destroy cancer cells will probably cause damage to some normal cells. Doctors adjust doses to do the least amount of harm possible to normal cells. Some patients feel few or no side effects, and others may have more serious side effects. In some cases, a dose adjustment is all that is needed to reduce or stop a side effect.

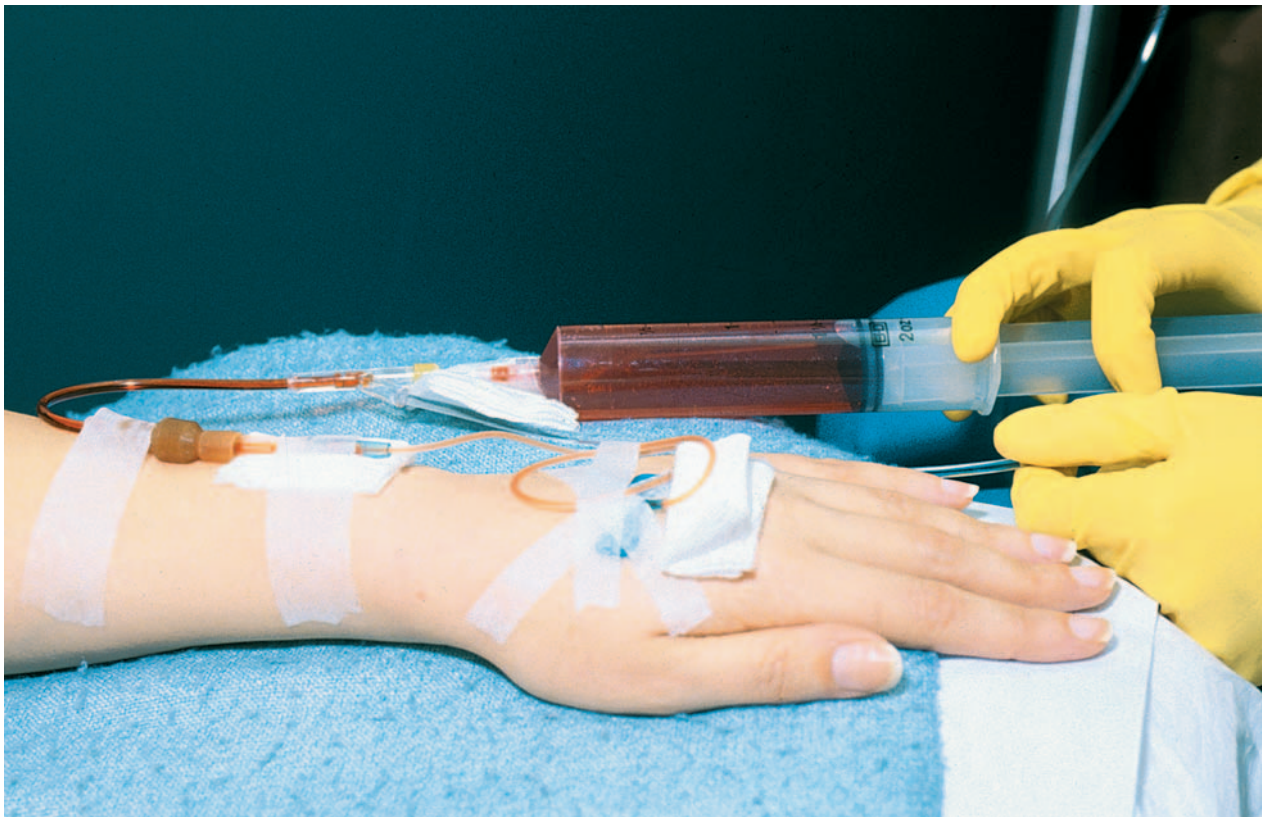
A person may experience a side effect right away or the reaction may be delayed. Side effects are classified as follows:

- acute, develops within 24 hours of treatment
- delayed, develops after 24 hours but within six to eight weeks of treatment
- short-term, combination of acute and delayed
- late/long-term, develops months or years after treatment, or lasts for an extended period of time
- expected, a side effect that develops in three quarters of patients
- common, occurs in 25–75% of patients
- uncommon/occasional, occurs in less than a quarter of patients
- rare, occurs in 5% of patients
- very rare, occurs in less than 1% of patients

Certain chemotherapy drugs have more side effects than others. While some drugs have immediate effects, other effects are delayed. Patients are encouraged to discuss the potential for side effects with their doctor. They must seek immediate medical attention if they are experiencing any unusual symptoms. Some of the most common side effects are discussed in this section.

Nausea and vomiting/loss of appetite

Nausea and vomiting are common, but can usually be controlled by taking antinausea drugs, drinking enough fluids, and avoiding spicy foods. Loss of appetite (**anorexia**) may be due to nausea or the stress of undergoing cancer treatment. Drugs that have a high likeli-



A woman receiving Adriamycin (doxorubicin) chemotherapy. *(Custom Medical Stock Photo. Reproduced by permission.)*

hood of causing nausea or vomiting include cisplatin, **mechlorethamine**, **streptozocin**, **dacarbazine**, **carmustine**, and dactinomycin. Those with moderate nausea-inducing potential include cyclophosphamide, doxorubicin, carboplatin, mitomycin, and L-asparaginase. Anticancer drugs with a low chance of causing nausea or vomiting include fluorouracil, methotrexate, etoposide, vincristine, and bleomycin.

Hair loss

Some chemotherapy drugs cause hair loss, but it is almost always temporary. Hair re-growth may not begin until several weeks have passed since the final treatment. This is the most common impact that chemotherapy has on the outer surfaces of the body. In some patients, an ice wrap, called an ice turban, can reduce hair loss. The effectiveness will depend on factors such as the type of drug, dose, and treatment schedule. This preventive treatment must be avoided by patients with leukemia, lymphoma, **mycosis fungoides** or by those with scalp tumors. People should use with caution if they have conditions such as vasculitis, cryoglobulinemia or a history of radiation to the head. Patients should discuss the ice turban treatment with their doctor before trying it.

Anemia and fatigue

Low blood cell counts caused by the effect of chemotherapy on the bone marrow can lead to anemia, infections, and easy bleeding and bruising. Patients with anemia have too few red blood cells to deliver oxygen and nutrients to the body's tissues. Anemic patients feel tired and weak. If red blood cell levels fall too low, a blood transfusion may be given.

Infections

Patients receiving chemotherapy are more likely to get infections. This happens because their infection-fighting white blood cells are reduced. The level of reduction can vary depending on the dose and schedule of treatments, and whether the drug is used alone or in combination with other anticancer agents.

It is important for chemotherapy patients to avoid infection. When the white blood cell count drops too low, the doctor may prescribe medications called colony

stimulating factors that help white blood cells grow. Neupogen and Leukine are two colony stimulants used as treatments to help fight infection.

Easy bleeding and bruising

Platelets are blood cells that make the blood clot. When patients do not have enough platelets, they may bleed or bruise easily, even from small injuries. Patients with low blood platelets should take precautions to avoid injuries. Medicines such as aspirin and other pain relievers can affect platelets and slow down the clotting process.

Sores in the mouth

Chemotherapy can cause irritation and dryness in the mouth and throat. An inflammation in the mouth is called **stomatitis**. Painful sores may form that can bleed and become infected. Precautions to avoid this side effect include getting dental care before chemotherapy begins, brushing the teeth and gums regularly with a soft brush, and avoiding mouth washes that contain salt or alcohol. Good oral hygiene is important. It is helpful for some patients to chew on ice chips for half an hour during chemotherapy treatments, but this should be discussed with the doctor before it is done.

Neuropathy and other damage to the nervous system

Cancer patients may develop neurological problems due to the cancer or the anticancer drugs. A variety of problems can develop, including altered mental alertness, changes in taste and smell, seizures, and peripheral **neuropathy** (tingling and burning sensations and/or weakness or numbness in the hands and/or feet). Different drugs can lead to different types of neurological disorders. Patients should discuss neurological symptoms with the doctor.

Heart damage

Some anticancer drugs are damaging to the heart. In these cases, the dosage is closely monitored in an attempt to avoid heart damage. Specific drugs that may be toxic to the heart include doxorubicin, daunorubicin, high doses of cyclophosphamide, and, in some cases, 5-FU. Patients experiencing chest pain or any cardiac symptoms should seek immediate medical help.

Kidney damage

A number of anticancer drugs can damage the kidney. Examples include high doses of methotrexate or 6-MP, as well as regular doses of L-asparaginase, cisplatin, mithramycin, streptozocin, and mitomycin C. Some kidney problems can be lessened by taking in adequate amounts of fluids. A secondary danger of kidney damage is that a less functional kidney can be more susceptible to further toxicity caused by other anticancer drugs that the patient is taking.

Respiratory problems

Cancer patients who have had radiation in the chest area are more susceptible to respiratory complications. Nitrosourea or bleomycin cause the most common type of respiratory toxicity, called pulmonary fibrosis. Patients should get immediate medical assistance if they have difficulty breathing.

KEY TERMS

Adjuvant therapy—Treatment given after surgery or radiation therapy when there is no further evidence of cancer to prevent the cancer from coming back.

Alkaloid—A type of chemical commonly found in plants and often having medicinal properties.

Alykylating drug—A drug that kills cells by directly damaging DNA.

Antiemetic—A medicine that helps control nausea; also called an anti-nausea drug.

Antimetabolite—A drug that interferes with a cell's growth or ability to multiply.

Combination chemotherapy—The use of two or more anticancer drugs over the same course of treatment.

Lumbar puncture—A procedure in which a person lies on his or her side and a doctor inserts a needle into the spinal column. It can be used to withdraw spinal fluid or to deliver chemotherapy into the spinal fluid.

Peritoneal cavity—The space between the two layers of the peritoneum, the membrane that covers the abdominal wall of the body.

Platelets—Blood cells that function in blood clotting.

Primary chemotherapy—Chemotherapy that is the primary form of treatment. It may be used to shrink a tumor prior to surgically removing it.

Sexual function

Some drugs can lead to impaired sexual function. Alkylating agents and **procarbazine** may result in the absence of sperm in a man and the lack of menstruation in a woman. Patients of child-bearing age are usually told to refrain from conceiving while undergoing chemotherapy because of the defects it can cause in the fetus.

Vision problems

Some anticancer drugs can impact a person's vision. High doses of cyclophosphamide can cause blurred vision in children, while some alkylating agents can cause cataracts. Tamoxifen may be damaging to the retina, and cisplatin can damage the optic nerve. Conjunctivitis, commonly called pinkeye, is a treatable problem that occurs with many anticancer drugs.

Results

The main goal of chemotherapy is to cure cancer. Many cancers are cured by chemotherapy. The chemotherapy treatment may be used in combination with surgery to keep a cancer from spreading to other parts of the body. Some widespread, fast-growing cancers are more difficult to treat. In these cases, chemotherapy may slow the growth of the cancer cells.

Doctors can tell if the chemotherapy is working by the results of medical tests. Physical examination, blood tests, and x rays are all used to check the effects of treatment on the cancer.

The possible outcomes of chemotherapy are:

- Complete remission or response. The cancer completely disappears for at least one month. The course of chemotherapy is completed and the patient is tested regularly for a recurrence.
- Partial response. The cancer shrinks in size by at least 30–50%, the reduction in size is maintained for at least one month, and no new lesions are found during treatment. The same chemotherapy may be continued or a different combination of drugs may be used.
- Minor response. The cancer shrinks 1–29%.
- Stabilization. The cancer does not grow or shrink. Other therapy options may be explored. A tumor may stay stabilized for many years.
- Progressive disease. The cancer continues to increase in size by at least 25%, or new lesions are noted. Other therapy options may be explored.
- A secondary malignancy may develop from the one being treated, and that second cancer may need additional chemotherapy or other treatment.

QUESTIONS TO ASK THE DOCTOR

- What type of anticancer drugs will be used?
- Why were these drugs selected?
- How will the drugs be administered?
- Where will the chemotherapy take place?
- What preparation is necessary before treatment?
- What are the side effects?
- How can side effects be lessened?
- What are the symptoms of dangerous side effects?
- Who will give the chemotherapy?
- How often will the chemotherapy be given?
- How often are blood tests needed between treatments?
- What special care is needed while undergoing this type of treatment?
- When will the treatments be completed?
- What is the expected result?

See also Cancer biology; Clinical trials; Complementary cancer therapies; Fatigue; Fertility issues; Infection and sepsis; Memory change; Metastasis; Nutritional support; Pregnancy and cancer.

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Chest x ray *see* **X ray**

Childhood cancers

Definition

Childhood cancers are malignant diseases that affect children under the age of 18 years.

Description

Cancer in children (pediatric cancers) differs from cancer in adults in several important ways. The most important difference is that children have generally better prognoses than do adults. Two-thirds of children with cancer are cured of the disease. Still, despite enormous progress in the treatment of childhood cancer since the 1960s, it is the second-most common cause of death in children older than one year, with accidents being the first.

One difference between pediatric and adult cancer is found in the cells in which the cancers originate. Many adult cancers begin in specific organs, such as a lung, the breast, or the colon. Childhood cancer, except for leukemias and brain tumors, often arise in connective tissues such as bone and muscle.

Childhood cancer is often more aggressive than adult cancers. It grows faster and is frequently metastatic (has moved to other parts of the body or to the major organs) by the time of diagnosis. Thus, surgery alone is less likely to cure a child. Nevertheless, the cancers children develop tend to be more responsive to **chemotherapy** and radiation than those of adults.

The median age for children at the time of a cancer diagnosis is six years; for adults it is 67 years. Most children with cancer are otherwise healthy; many adults have conditions, such as heart disease, that make their treatment and recovery more difficult. Another important difference is that screening tests are available for some adult cancers, such as mammograms for **breast cancer** and Pap smears for **cervical cancer**. There are no useful screening tests for childhood cancers. Not infrequently, the diagnosis is made at a routine pediatric visit.

An extremely important factor in the improved prognosis of children with cancer has been the enrollment of the majority of children with cancer in research trials. Although only 2% of all cancers diagnosed in the United States occur in children, more than 70 percent of those children are enrolled in formal research protocols. By contrast, although adults have 98% of all cancers diagnosed in the United States, only 3% enroll in trials. Research protocols permit rapid collection of data on the effectiveness of treatment; they recognize adverse effects quickly, and foster valuable communication and collaboration among pediatric oncologists throughout the country and the world. In 1998, the four major pediatric research consortia in the United States joined forces. The Pediatric Oncology Group, the Children's Cancer Group, the Intergroup **Rhabdomyosarcoma** Study Group, and the National **Wilms' Tumor** Study Group, combined to form the Children's Oncology Group—to the great benefit of children with cancer.

Demographics

About 8,700 cases of cancer are diagnosed in children under the age of 15 years in the United States each year. Another 2,000-3,000 are diagnosed in teenagers over 15 years of age, but these are often recorded with adult diagnoses. The number of cases of childhood cancer has remained steady for a number of years. Researchers estimate that 1 of every 333 children will be diagnosed with cancer before the age of 20 years.

Leukemia accounts for 31% of the cancers in children, with about three-quarters of those being **acute lymphocytic leukemia** and the other one-fourth mostly acute myelogenous leukemia. Central nervous system (CNS) cancers, commonly lumped together as brain tumors, are the next largest group, constituting another 17%. **Lymphoma**, both Hodgkin's and non-Hodgkin's, accounts for 15 percent of childhood cancers. The rest of the diagnoses are divided among what are referred to as solid tumors, such as **neuroblastoma**, **retinoblastoma**, Wilms' tumor, rhabdomyosarcoma, and bone cancers.

These statistics are similar in other parts of the developed world. In Africa, the most common form of

childhood cancer is **Burkitt's lymphoma**, which is associated with the Epstein-Barr viral infection.

The survival rate for children with cancer is approaching 80% in the United States.

Causes

The causes of most childhood cancers are unknown, but some associations are recognized. The risk of childhood leukemia is increased in children with Down syndrome, in boys, in whites, and in those of higher socioeconomic status. Exposure to radiation *in utero* increases the risk as well. Central nervous system cancers are also more common in boys, in whites, and in those who have received radiation treatments for other cancers.

A number of inherited and developmental conditions are associated with an increased risk of childhood cancer. These include neurofibromatosis, Bloom's syndrome, ataxia-telangiectasia, and tuberous sclerosis. A family history of **Hodgkin's disease** increases its likelihood, and a family history of retinoblastoma in both eyes confers a 50% chance of an offspring carrying the gene. Ninety percent of children carrying the gene will develop the disease.

Special concerns

Family

Few situations test a family or a marriage like a diagnosis of cancer in a child. One day, parents have a healthy child with unlimited potential and a bright future; the next day, they have a child with a possibly fatal disease.

With a diagnosis of cancer in a child, parents must begin to negotiate complicated medical, social, family, and financial issues. Because children are generally best treated in centers that have pediatric oncologists, and because such centers can be far from a family's home, whole families can be uprooted, parents forced to spend weeks apart, and siblings left home with other relatives for long stretches of time.

Guilt can consume parents. They often assume they are responsible for their child's illness, they feel guilty if finances or insurance coverage issues force both to remain employed during their child's illness, and they worry that they are neglecting their other children.

One of the most difficult aspects of dealing with a diagnosis of cancer in a child is deciding what to tell that child and when. For infants and toddlers, this is not a concern, but older children need to know that they are ill, that they need these painful and unpleasant treatments, and—importantly—that they are not being punished for some misdeed, which is a common fear.

School

More than 80% of children with cancer miss at least some school during their treatments. Some children must miss school for prolonged periods. Federal law requires all states to provide education to handicapped children, and children with cancer are considered handicapped under the law. An individual education plan must be developed and an education provided, even for those who are homebound due to illness. Hospital social workers can be good resources for parents to explore their children's rights under their state's laws.

Completion of treatment

One of the surprisingly difficult aspects of cancer treatment comes when the treatment itself is completed. Parents, and certainly older children, can find the loss of the routine of regular treatment and the comfort of knowing that something active is being done to keep the cancer at bay can be quite frightening. Some parents and children become excessively focused on minor symptoms, fearful of recurrence. Occasionally, children who survive cancer become risk-takers as they grow, engaging in dangerous sports or hobbies.

Death

Though the survival rates for children with cancer continue to improve, the tragic truth is that some children will die of their disease. For parents, the day they learn that no further treatment is available is even harder than the day they learned their child's diagnosis. No decision is more difficult than stopping futile treatment and turning to care that is palliative (aimed solely at making the child comfortable).

Hospice care can be a valuable part of the end-of-life treatment for a child with cancer. Though not all inpatient hospice facilities accept children, they do provide home hospice care. Most families find that bringing their terminally ill child home, letting the child die in familiar surroundings with their loved ones at their side, offers them the only comfort to be had in a time of great sadness.

Grief for the death of a parent or spouse can last for months or even years, but most adults eventually come to accept those losses. Grief for the death of a child is life long. One of the hardest tasks for a parent in mourning can be offering the necessary support and love to their other surviving children. Some parents who lose a child to cancer can find some solace from support groups. Such groups are available through hospitals, hospices,

churches, counseling, and cancer organizations. Other parents prefer solitude and time to face their loss.

Treatments

The treatment of childhood cancer depends on the specific disease, what tissues are affected, and how extensively it has spread at the time of diagnosis.

Acute lymphoblastic leukemia and acute myelocytic leukemia

Acute lymphoblastic, or lymphocytic, leukemia (ALL) is the most common form of cancer in children, occurring about three times as often as **acute myelocytic leukemia** (AML). Leukemia of either type causes symptoms such as fevers, pallor, **fatigue**, bleeding or bruising, swollen glands, and bone pain—which can manifest itself as a limp or refusal to walk.

The diagnosis is made based on blood tests and bone marrow studies. The treatment is similar for both types. ALL has a very good prognosis, with a cure rate of about 80%; AML has a poorer prognosis, with different studies citing cure rates of 35-55%.

Treatment for ALL requires prolonged chemotherapy, consisting of remission induction, consolidation or intensification therapy, and maintenance. An essential component of the successful treatment of ALL is prophylactic (preventative) treatment to the CNS, a common site of relapse. In the past, children received radiation to the CNS, but this carried a risk of later brain tumors and significant neurologic and psychiatric deficits. Only the highest risk children now receive CNS radiation; the rest receive intrathecal chemotherapy, which means that the medications are introduced directly into the spinal fluid during spinal taps.

Similar strategies are used in children with AML, but since far more of these patients relapse, **bone marrow transplantation** becomes an important option.

Non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma constitutes about 60% of the lymphomas in children, and 10% of all childhood cancers. It is a cancer of the lymphatic system, which includes the spleen and lymph nodes. It is more common in boys than in girls, and other risks for the development of non-Hodgkin's lymphoma include conditions that depress the immune system, such as AIDS or immune suppressive treatment after organ or bone marrow transplant. Many such cases are Burkitt's lymphomas, and are associated with the presence of **Epstein-Barr virus**. These often manifest as masses in the jaw.

Non-Hodgkin's lymphoma has survival rates of 60-90%, depending upon the stage at which it is diagnosed. Lymphoma might be found at a routine examination, with nothing but swollen lymph nodes or an enlarged spleen as early signs. Some children do experience fevers or drenching **night sweats**, while others complain of persistent **itching**. Like adults, some teenagers will experience unexplained abdominal pain with alcohol ingestion, but might never report this symptom to parents for fear of consequences for underage drinking.

Non-Hodgkin's lymphoma is treated with chemotherapy, with radiation generally reserved for emergency treatment of bulky tumors that threaten other organs.

Hodgkin's disease

Hodgkin's disease is rare in young children but becomes more common in the teen years. Early Hodgkin's disease is one of the most curable of all cancers, with a cure rate as high as 95%. Early disease is often treated with chemotherapy alone, while more advanced disease is often treated with both chemotherapy and radiation.

Central nervous system cancers

CNS tumors account for about 17% of all childhood cancers. Several major categories of brain cancers are found in children.

MEDULLOBLASTOMA This is the most common brain tumor found in children. Its symptoms can appear as headaches, **nausea and vomiting**, and it can also cause gait disturbances and damage to the cranial nerves (those nerves that control such functions as eye movement and facial muscle control). **Medulloblastoma** is treated by surgical removal of the tumor and postoperative radiation. Chemotherapy appears to improve survival rates in those children with the most advanced disease at the time of diagnosis.

GLIOMA These arise most often in the brainstem, at the base of the brain. Those that arise in the segment of the brain known as the pons have the poorest prognosis. Many gliomas produce gait abnormalities and cranial nerve problems such as double vision, and swallowing and speech disorders. Their location makes them difficult to reach surgically, so the primary treatment is **radiation therapy**. Most trials of chemotherapy have not shown benefit, but newer agents are being explored.

High-grade malignant gliomas include astrocytomas and glioblastomas. They are treated by surgical removal when possible, radiation therapy, and sometimes chemotherapy.

EPENDYMOMA These cancers arise in the cells that line spaces within the brain—known as the ventricles—or the spinal column. In addition to nausea, vomiting, and headache, an ependymoma can cause head tilting and hearing loss. Treatment consists of surgery to remove the tumor followed by radiation. Chemotherapy does have benefit in children under three years of age but has less value in older children.

Neuroblastoma

Neuroblastoma, which accounts for about 8% of all childhood cancers, is far more common in infants than in older children. It originates in the sympathetic nervous system, a complicated system involving nerves and the adrenal glands, which produce hormones such as epinephrine and norepinephrine (also called adrenaline and noradrenaline). Most neuroblastomas arise in the adrenal glands, and are noticed as a mass in the abdomen. However, they can arise anywhere in the sympathetic nervous system, appearing as masses in the neck, the chest, or the pelvis.

Symptoms are usually related to whatever organs are compressed by the growing tumors. Thus, abdominal masses produce discomfort, vomiting or loss of appetite. Neck masses can press on certain nerves and cause an eyelid to droop, the pupil to constrict, and the eye to stop producing tears. Masses in the pelvis can cause constipation or urinary retention. Because these cancers arise in tissues that produce epinephrine and similar substances, symptoms may be related to high levels of those substances. Children might be noted to sweat, flush, become pale, complain of palpitations or a rapid heartbeat, or develop high blood pressure.

Neuroblastomas are staged based on the age at diagnosis, location of the tumor, and degree of spread. Children considered at low or intermediate risk have the best prognoses, with up to 90% achieving long-term survival. Those at the highest risk have traditionally had a poor prognosis, with only about 15% surviving. The use of more intensive chemotherapy had improved the survival rate to 30% 1995.

Treatment consists of surgery to remove as much tumor as possible, chemotherapy, and often radiation therapy.

Wilms' tumor

Wilms' tumor, or nephroblastoma, is a cancer that arises in the kidney. It accounts for 5% of all cancers in children. Signs and symptoms of Wilms' tumors include abdominal masses, abdominal pain or swelling, high blood pressure, and blood in the urine—either visible or in microscopic examination. Treatment consists of removal of the kidney along with the tumor. Many children also receive radiation or chemotherapy, depending upon the extent of the original disease and the specific cell types involved. Wilms' tumors diagnosed at the very earliest stages have extremely favorable prognoses, with as high as a 98% cure rate.

Sarcomas

Soft tissue **sarcomas** are broadly divided into rhabdomyosarcoma and nonrhabdomyosarcoma soft tissue sarcomas. These are cancers of connective tissue. Rhabdomyosarcomas constitute about half of these types of cases. It is the fourth most common solid tumor in children, after brain tumors, neuroblastoma, and Wilms' tumor. It begins most commonly in sites in the head and neck, but can also arise in the urinary tract and the extremities. Symptoms can vary depending on the site of origin but, most often, rhabdomyosarcoma develops as a painless mass.

The nonrhabdomyosarcomas arise in a variety of different cell types. Among those cell types are the cells of the linings of peripheral nerves, the linings of joints, and other fibrous tissue. The most common sites of origin are the limbs, the trunk, the abdomen, and the pelvis.

The prognosis of both types of sarcomas varies with the extent of spread at the time of diagnosis and the type of cell from which the cancer arose. About 90% of children with early stage sarcomas can be cured, while only 20% of those with the most advanced disease at the time of diagnosis can be cured. Treatment consists of surgery and chemotherapy.

Osteogenic sarcoma

This is a form of bone cancer. In the past, all such cancers were treated with **amputation**. Now, **limb salvage** surgery can be performed in a number of cases. Chemotherapy and surgery combined have improved the prognosis for this disease to a 60% long-term survival rate.

Ewing's sarcoma

Ewing's sarcoma is a rare bone cancer that usually occurs in teenagers. It is more common in girls than in boys, and often starts in the femur (thighbone). Between 50 and 60% of children with Ewing's sarcoma will survive up to five years.

Retinoblastoma

Retinoblastoma is a cancer that arises in the cells of the retinas of the eyes. It is a disease of young children and has been diagnosed at birth. It can occur in both eyes in an inherited syndrome, and siblings of children with retinoblastoma in both eyes need to be screened. First symptoms include a sudden onset of squinting or crossed eyes. Radiation therapy will cure the disease in about

90% of children and, although most will suffer some visual changes, few lose their eyesight.

Germ cell cancers

These include teratomas, choriocarcinomas, embryonal carcinomas, and germinomas. These are all cancers of stem cells—cells that represent the earliest, or embryonal, stages of cell development and which have the potential to develop into mature cells. Some **germ cell tumors** are benign; others are malignant. They arise in the ovaries, testes, or sites along the midline of the interior of the body. Symptoms vary with the site of origin. Testicular masses are usually painless; ovarian masses can be accompanied by abdominal pain and swelling. Midline germ cell cancers can cause constipation or urinary retention as they grow and block internal organs. They are treated with surgery, radiation, and chemotherapy, and long-term survival rates are as high as 80% percent.

Hepatic cancers

Hepatic (liver) cancers are rare but not unheard of in children. There are two types of liver cancer in children. Hepatoblastoma, which accounts for about two-thirds of these, is associated with familial polyposis, an inherited disease of multiple polyps in the colon. It has also been associated with fetal alcohol syndrome. Its incidence has risen since the 1970s.

The second type is hepatocellular **carcinoma**, which accounts for about one-third of the cases of liver cancer in children, and its incidence has been falling. Hepatocellular carcinoma has been associated with hepatitis B and C, exposure to anabolic steroids, aflatoxins (food contaminants), pesticides, and vinyl chloride.

Treatment of both of these cancers includes surgical removal of the cancer and chemotherapy, although hepatoblastoma is more responsive to chemotherapy than is hepatocellular carcinoma.

Alternative and complementary therapies

Alternative and complementary treatments have not been studied extensively in children, and some have been proven harmful. Herbal remedies can be particularly dangerous, in that children have very different metabolisms from adults and relatively benign treatments for adults can be fatal in children. For example, *jin bu hua*, a traditional Chinese medicine, can produce heart problems or difficulty breathing. Life root or comfrey might cause fatal liver damage in children.

Techniques such as guided imagery can be adapted for children. Providing favorite toys or videotapes can serve as focal points for children to distract them from painful or frightening procedures.

Late effects of treatment

The high cure rates for children with cancer have not come without a price. While chemotherapeutic drugs and radiation are highly toxic to cancer cells, they are highly toxic to healthy cells and organs, as well. Most organ systems can be affected by cancer treatment, and children who have been cured of cancer frequently face lifelong consequences of those treatments.

Organ systems

CENTRAL NERVOUS SYSTEM Children who receive radiation therapy to their brains often experience a decline in scores on cognitive tests. More than one-half of the children who receive high-dose brain radiation have IQ scores below 90. Children with **acute leukemia** who are given chemotherapeutic agents directly into their spinal fluid are also at risk for developing learning disabilities and other neurologic effects.

EYES AND VISION Both radiation to the brain and chemotherapy can cause damage to vision. If the eyes are included in a radiation field, the child can develop radiation cataracts. The long-term use of steroids, which are part of most chemotherapeutic regimens and used after bone marrow transplant, can also cause cataracts.

HEARING Both radiation and the drug, **cisplatin**, can cause hearing loss.

TEETH AND SALIVARY GLANDS Radiation therapy to the head and neck can damage permanent teeth and salivary glands. The chemotherapy administered to very young children with acute lymphoblastic leukemia can also cause damage to the teeth.

HEART Heart damage can occur from the toxic effects of radiation therapy and from certain chemotherapeutic drugs. That damage can be centered in the heart muscle, the pericardium (lining) of the heart, or the coronary arteries. The drugs most noted for causing heart damage are **daunorubicin** and **doxorubicin**. They do particular damage to the left ventricle, the main pumping chamber of the heart. This can lead to congestive heart failure, in which the heart fails to pump blood effectively throughout the body. This might not appear until later life, precipitated by such stressors as vigorous exercise or pregnancy. Some survivors of childhood (and adult) cancers eventually come to require heart transplant.

LUNGS **Bleomycin** and **carmustine**, two chemotherapeutic drugs, can cause inflammation of the lungs with later scarring and decrease in lung function. Radiation treatment of the chest can also impair lung function.

KIDNEYS The kidneys can be damaged by radiation therapy to the abdomen or by a number of chemotherapeutic drugs. Some of those drugs are cisplatin, BCNU, **ifosfamide**, **methotrexate**, **vinblastine**, and bleomycin. Children treated for Wilms' tumors can develop kidney disease in the unaffected kidney years after treatment.

BLADDER Radiation to the pelvis combined with the drug **cyclophosphamide** can produce a cystitis or bladder inflammation.

LIVER Liver damage can occur with radiation or with chemotherapy. The agents used to treat leukemias are particularly known for their liver toxicity. BCNU is another agent with known liver toxicity.

Because so many children receive transfusions of blood products, they are at risk for developing transfusion-related hepatitis, which can progress to cirrhosis in a few cases. Blood products are now screened for the presence of hepatitis B and C viruses, but many older surviving children received transfusions before the screening tests were available.

SMALL INTESTINE Radiation can cause an acute inflammation of the intestines with vomiting and **diarrhea**. Some children go on to develop scarring of the intestines that can lead to blockages requiting surgical repair.

MUSCULOSKELETAL SYSTEM Radiation to the spine, sometimes used for children with Hodgkin's disease or medulloblastoma, can produce curvature of the spine, in the form of kyphosis, or hunchback, or scoliosis, an S-shaped curve of the spine. Radiation to the hips can cause damage to the hipbones. The two most common forms of that damage are slipped capital femoral epiphysis and avascular necrosis, both of which involve damage to the end of the thighbone where it meets the pelvic bones.

Loss of the necessary minerals within the bones can be seen in children who have been treated for brain cancers, acute lymphoblastic leukemia, lymphoma and some solid tumors. Long term use of steroids or methotrexate is a common cause of this. These children are at risk of fractures.

ENDOCRINE SYSTEM The endocrine system is the group of glands responsible for the production of hormones. Almost any gland can be affected.

Pituitary gland: Brain radiation can cause growth hormone deficiency. Even when normal levels of growth hormone are found, children who have undergone brain radiation are often obese and fail to achieve their expected height. Those whose levels are low will grow when growth hormone injections are administered.

Thyroid gland: The thyroid gland can be damaged by radiation treatment that involves the neck, typically becoming underactive. This might not occur until several years after treatment, and is treated with oral thyroid hormone.

Reproductive function: Radiation therapy and chemotherapy can both damage the ovaries, causing loss of hormones, lack of periods and infertility. The testes are less easily damaged and adult male survivors often have normal hormonal levels and sexual function, but might be sterile. Adolescents might be offered the opportunity to bank sperm before treatment to ensure that they might have future children through artificial insemination. Those who have had surgery to remove internal nodes involved in **testicular cancer** might be impotent as adults due to damage to the nerves that control sexual function.

Concerns have been raised that since chemotherapeutic agents can cause genetic mutations, those survivors whose fertility has been preserved might be at risk of giving birth to children with birth defects. This has not been observed yet, but children of women treated for Wilms' tumors often have low birth weights.

Second cancers

The most serious late effect of successful treatment for childhood cancer is a second cancer. **Second cancers** are a different type and are related to either inherited factors or, far more often, to late effects of treatments.

GENETIC CAUSES About fifty percent of those who have been treated for the hereditary form of retinoblastoma develop a second cancer at some point in their lives.

SURGICAL TREATMENT Children with cancers that obstruct the flow of urine sometimes require a procedure called ureterosigmoidostomy. In this, the ureter, which carries urine from the kidney to the bladder, is attached instead to the sigmoid colon. Such children have a significant risk of developing adenocarcinoma of the colon at the site of the connection in adulthood.

RADIATION THERAPY Radiation to the neck can cause later **thyroid cancer**. Radiation to the brain can cause later brain tumors, such as meningiomas or gliomas. This was once fairly common in children treated for leukemia and given prophylactic radiation therapy to prevent central nervous system relapse. Bone sarcomas are possible after radiation treatment of retinoblastomas or Ewing's sarcoma. The risk of later breast cancer is increased in those who were treated with radiation for Hodgkin's disease in childhood.

CHEMOTHERAPY **Etoposide** and **teniposide**, chemotherapeutic drugs known as epipodophyllins, are

associated with a risk of developing acute myelogenous leukemia in the years after initial treatment for cancer. These are used in treatment of some germ cell tumors, ALL, and non-Hodgkin's lymphoma.

IMMUNE SUPPRESSION To prevent rejection, children who undergo bone marrow transplant receive drugs to suppress their immune systems. Long-term use of these medications is associated with a risk of developing cancer that originates in the white blood cells known as B cells.

See also Cancer genetics; Extragonadal germ cell tumor; Osteosarcoma.

KEY TERMS

Ataxia-telangiectasia—An inherited disorder of abnormal gait, skin lesions, and respiratory infections associated with a greater-than-average risk of developing childhood cancer.

Bloom's syndrome—An inherited disorder featuring skin abnormalities with a higher-than-average risk of childhood cancers.

Connective tissues—Those parts of the body that give it structure and form, including bones, joints, muscles, tendons, and ligaments.

Familial polyposis—An inherited disorder featuring multiple polyps in the colon with a very high likelihood of developing colon cancer by age 40; also associated with a greater-than-average risk of developing childhood cancer.

Fetal alcohol syndrome—A variety of birth defects that occur in children of mothers who abuse alcohol while pregnant, including mental retardation and facial abnormalities. Children with this syndrome have a higher than average risk of developing liver cancer.

Neurofibromatosis—An inherited disorder characterized by skin lesions, including brown spots called café au lait spots, small to large skin tumors, and neurofibromas, tumors within nerves. This carries a higher than average risk of developing childhood cancer.

Pituitary gland—The gland that produces multiple hormones that in turn affect other glands. The pituitary influences the nerves, the thyroid gland, the adrenal glands, and the ovaries and testes.

Tuberous sclerosis—An inherited disorder that includes skin abnormalities, mental retardation, and seizures, and carries a higher-than-average risk of childhood cancer.

Ureterosigmoidostomy—A surgical procedure that reroutes the ureters, the tubes that carry urine from the kidneys to the bladder, by implanting them instead into the sigmoid colon.

Ventricles—Spaces within the body. In the brain, these are spaces filled with cerebrospinal fluid. In the heart, these are the largest pumping chambers.

Resources

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Road, Atlanta, GA, 30329. (800)ACS-2345. <http://www.cancer.org>.

Cancer Care, Inc. 1180 Avenue of the Americas, New York, NY 10036. (212)302-2400 or (800)813-4673. <http://www.cancercare.org>.

Candlelighters Childhood Cancer Foundation. 7910 Woodmont Avenue, Suite 460, Bethesda, MD 20814. (800)366-CCCF. <http://www.candlelighters.org>.

QUESTIONS TO ASK THE DOCTOR

- What type of cancer does my child have?
- What characteristics of my child's illness are favorable? Which are unfavorable?
- What course of therapy do you recommend?
- What medications will you use and what side effect should we anticipate?
- Will my child require surgery?
- Will my child need radiation therapy?
- Will my child need to be hospitalized for treatments?
- Should my child be enrolled in a clinical trial?
- Should my child be treated at a pediatric oncology center?
- Can my child continue to go to school?
- Can I stay with my child for procedures; for hospitalizations?
- How and what should we tell our child about the illness?
- What should we tell our other children?
- What should we expect after treatment is finished?

Childhood Cancer Ombudsman Program. P.O. Box 595, Burgess, VA 22432. Fax: (804)580-2502

The Leukemia and Lymphoma Society of America (formerly The Leukemia Society of America). 1311 Mamaroneck Avenue, White Plains, NY 10605. (914)949-5213. <http://www.leukemia-lymphoma.org/>.

The National Cancer Institute. Cancer Information Service. Building 31, Room 10A31, 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (301)435-3848. <http://www.nci.nih.gov/>.

National Childhood Cancer Foundation. 440 E. Huntington Drive, P.O. Box 60012, Arcadia, CA 91066-6012. (626)447-1674. <http://www.nccf.org>.

National Marrow Donor Program. Suite 500, 3001 Broadway Street NE, Minneapolis, MN 55413-1753. (800)MARROW2 (800-627-7692). <http://www.marrow.org/>.

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Marianne Vahey, M.D.

Chlorambucil

Definition

Chlorambucil (marketed under the brand name Leukeran) is a **chemotherapy** medicine used to treat cancer by interfering with the growth of cancer cells.

Purpose

Chlorambucil is approved by the Food and Drug Administration (FDA) to treat **chronic lymphocytic leukemia** and malignant lymphomas. It has also been less commonly used for other types of cancer including **breast cancer**, **ovarian cancer**, and choriocarcinoma. Chlorambucil is not used with the intent to cure the cancer but to improve symptoms of the disease.

Description

Chlorambucil is a member of the group of chemotherapy drugs known as alkylating agents. Alkylating agents interfere with the genetic material (deoxyribonucleic acid, or DNA) inside the cancer cells and prevent them from further dividing and growing more cancer cells. Chlorambucil is a tablet that is taken orally.

Recommended dosage

Chlorambucil can be taken according to several different dosing schedules, depending on the disease to be treated. Chlorambucil is a 2mg oral tablet, and patients

may need to take more than one tablet at a time depending on the dose. The dose is based on a patient's weight in kilograms. Patients with leukemia take chlorambucil daily for three to six weeks at a dose of 0.1 to 0.2 mg/kg/day (milligram per kilogram of body weight per day).

Precautions

Patients who have received a full course of **radiation therapy** or chemotherapy generally should not receive chlorambucil until four weeks after the radiation or chemotherapy has been completed. Heath care providers should be notified if patients have had any previous allergic reactions to chemotherapy treatment. Patients should also increase the amount of fluids that they drink while on this medicine.

Blood counts will be monitored regularly while on chlorambucil therapy. During a certain time period after receiving chlorambucil there may be an increased risk of getting infections. Caution should be taken to avoid unnecessary exposure to infectious agents. Patients should check with their doctors before receiving live virus **vaccines** while on chemotherapy.

Patients who may be pregnant or trying to become pregnant should tell their doctor before receiving chlorambucil. Men and women undergoing chemotherapy are at risk of becoming sterile.

Side effects

The most common side effect from taking chlorambucil is **myelosuppression**, a suppression of bone marrow activity resulting in a low blood cell count. Myelosuppression is usually the goal when treating leukemia with chlorambucil. When the white blood cell count is lower than normal (leukopenia), patients are at an increased risk of developing a **fever** and infections.

The platelet count can also be decreased due to chlorambucil administration. Platelets are blood cells normally found in large numbers that aid in clot formation. When the platelet count is low, patients are at an increased risk for bruising and bleeding. If the platelet count remains too low, a platelet blood transfusion is an option for treatment. More rarely, chlorambucil causes a condition called **anemia** in which the number of circulating red blood cells drops, resulting in dizziness and/or **fatigue**. **Erythropoietin** is a drug that can be used to increase the red blood cell count.

Less common side effects from chlorambucil include nausea, vomiting, loss of appetite, mouth sores, skin rashes, and **diarrhea**. **Antiemetics** may be given to patients before taking chlorambucil to help prevent or reduce **nausea and vomiting**. Liver problems may occur due to chlorambucil administration, but they are typically mild and resolve when the drug is stopped.

Damage to nerves and nervous system tissues is uncommon with chlorambucil therapy. Some reports do exist of nerve damage that has resulted in seizures, muscle twitching, muscle shaking, confusion, visual hallucinations, irritability, and loss of muscle control. Other rare reactions to chlorambucil include hair loss (**alopecia**), **itching**, fever, lung problems, eye problems, tingling of the hands and feet, cystitis (bladder infection), and the development of another type of cancer or leukemia.

Interactions

There are no significant drug interactions associated with taking chlorambucil.

Nancy J. Beaulieu, RPh., BCOP

KEY TERMS

Anemia—A reduction in the normal number of red blood cells in the blood.

Chemotherapy—Specific drugs that are used to treat cancer.

Cystitis—An irritation of the bladder lining.

DNA—Deoxyribonucleic acid; genetic material inside of cells.

Food and Drug Administration—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives the approval to pharmaceutical companies for commercial marketing of their products.

Intravenous—Entering the body through a vein.

Leukopenia—A reduction in the normal number of white blood cells in the blood.

Metastatic—Cancer that has spread to one or more parts of the body.

Cholangiocarcinoma *see* **Bile duct cancer**

Chondrosarcoma

Definition

Chondrosarcoma is a malignant tumor that arises from cells that produce cartilage, the rubbery tissue

around joints. Therefore, it is a type of sarcoma that is predominantly found in the area around bones.

Description

Sarcomas of the bone are rare and represent about 0.2% of all new cancer cases each year. The two most common forms of bone cancer are **osteosarcoma** and **Ewing's sarcoma**. Among the less common are chondrosarcoma, **fibrosarcoma**, and **malignant fibrous histiocytoma**, all of which arise from spindle cell neoplasms.

Chondrosarcomas arise from chondroblasts, cells that form cartilage. Cartilage is the matrix found at the tip of the nose and ears. However, cancer that develops from chondroblasts is usually observed on the surface of the pelvis, in the femur of the upper leg, around the shoulder, in the humerus of the upper arm, and in the ribs.

Depending on the type and location of the chondrosarcoma, the tumor can either be high grade and aggressive or low grade and not as invasive. There are two different categories of chondrosarcomas—classic chondrosarcomas and variant chondrosarcomas. Together they have five main types.

Central chondrosarcoma and peripheral chondrosarcoma are both classic chondrosarcomas. Central chondrosarcoma occurs within a bone, and peripheral chondrosarcoma develops on the surface of a bone. Both can develop as a primary tumor or as a secondary tumor to an existing tumor elsewhere in the body. Most, however, are primary tumors. Seventy-six percent of primary chondrosarcomas occur centrally within a bone.

There are three variant chondrosarcomas: clear cell chondrosarcoma, mesenchymal chondrosarcoma, and dedifferentiated chondrosarcoma. Clear cell chondrosarcoma is the most rare form of chondrosarcoma. It is a low grade, slow growing tumor that typically occurs locally in the epiphysis, or end part, of long tubular bones such as the femur and humerus, meaning that it does not normally invade into surrounding soft tissue. As the name implies, cells biopsied from this type of chondrosarcoma appear clear with many large vacuoles.

Mesenchymal chondrosarcoma is another rare variant. However, as opposed to clear cell chondrosarcoma, it is highly malignant and frequently metastasizes, commonly to the lungs, lymph nodes and other bones. This variant has a tendency to develop in flat bones such as vertebra, the pelvis, or the skull, as opposed to long tubular bones. Under a microscope, the cells appear round and contain spindle cell elements and neoplastic cartilage formation.

Dedifferentiated chondrosarcoma is also rare and is the most malignant form of chondrosarcoma. It is characterized by the presence of a mix of low-grade chondrosarcoma and has undergone malignant degeneration, producing a fully malignant soft tissue mass that is no longer identifiable as cartilage. These cancers occur most commonly in the flat bones of individuals over the age of sixty. Despite varied treatments, they are almost always fatal.

Due to the location of chondrosarcoma tumors, the result is often a decrease in the range of motion of limbs, especially tumors occurring on the epiphysis of bones such as those seen in clear cell chondrosarcoma.

Demographics

Although there are exceptions, chondrosarcomas occur mainly in older adults forty to sixty years old and typically occur more in men than in women. Chondrosarcomas are rarely seen in infants and children. Dedifferentiated chondrosarcomas predominantly arise in the elderly over the age of sixty, equally between males and females. Mesenchymal chondrosarcoma develops in the young adult population between the ages of twenty and forty years old, and it is slightly more common in females. Classic chondrosarcomas usually develop in people over the age of forty. However, when they occur in younger age groups, they have a propensity to be highly malignant, capable of **metastasis**.

Causes and symptoms

As of 2005, there is little known about what causes chondrosarcomas. However, researchers have discovered that chondrosarcomas are sometimes associated with underlying benign bone tumors. They can also result as a side effect from previous **radiation therapy** for unrelated primary cancer treatment. Individuals with other bone diseases such as Maffucci's syndrome and Ollier's disease are at a higher risk for developing chondrosarcomas.

There are many symptoms associated with the onset of chondrosarcomas. They tend to develop slowly in most cases, except when the cancer is aggressive. The following is a list of the main symptoms that may present:

- pain
- swelling
- firm lump
- broken bone
- impeded normal range of motion
- urinary frequency (seen in pelvic chondrosarcomas)
- urinary obstruction (seen in pelvic chondrosarcomas)

The above symptoms are not always indicators of the presence of chondrosarcoma. Any one of these symptoms could be related to another, less serious condition. A doctor should be seen to diagnose the problem properly.

Diagnosis

In order to diagnose bone cancer, a doctor will take the patient's history and conduct a thorough physical exam. Blood tests will be performed to rule out other conditions and identify cancer markers.

The most revealing initial exam is an **x ray**. It can show the location, size, and shape of the tumor. If a malignant tumor is present, the x ray will expose a soft tissue mass with ill-defined edges. This procedure takes less than an hour and can be performed in the doctor's office. Depending on the medical facilities, the results can be returned the same day after being interpreted by a physician, and perhaps a consulting oncologist and radiologist.

Once there is evidence of a tumor, one or more of several other procedures may be performed, including CT scans, MRI (**magnetic resonance imaging**), angiograms, and **biopsy**.

Treatment team

If the patient is seeing a primary care provider, the provider may perform the initial diagnostic tests. However, in order to comprehensively diagnose and treat chondrosarcomas, the primary care provider will refer the patient to an orthopaedic oncologist (bone cancer specialist). Radiologists, pathologists and orthopaedic surgeons will also be involved to read x rays, examine tissue samples, and remove the tumor if necessary.

Many other individuals will be involved with the treatment of chondrosarcoma. For example, nurses and dieticians are available to explain side effects of treatment and offer suggestions on eating healthy meals to help fight the side effects. If a limb is totally or partially removed, a physical therapist or vocational therapist will assist the patient in learning how to use a prosthetic limb.

Clinical staging, treatments, and prognosis

After the physician makes the diagnosis, it is important to determine the stage of the cancer. This will help reveal how far the cancer has progressed and how much tissue has been affected.

A new system of staging was adopted in 1980 by the Musculoskeletal Tumor Society. It is based on the fact that differing tissue types associated with the bone behave similarly when cancerous. This classification system uses grade (G), location (T), and lymph node involvement and metastasis (M).

KEY TERMS

Carcinogen—An agent that is capable of causing cancer.

Epiphysis—The end of long tubular bones such as femur in the leg and the humerus in the arm. Initially separated from the main bone by a layer of cartilage that eventually allows the parts to fuse.

Spindle cells—Spindle-shaped cells typically found in connective tissue.

Surgical grade (G) refers to how aggressive the cancer is. For example, G0 represents a benign tumor and G2 represents a highly aggressive tumor. The anatomical location (T) establishes whether or not the tumor is inside the bone (T1) or outside the bone (T2). If metastases are present, then the tumor is classified as M0; and if metastases are not present, the tumor is classified as M1. The following is a list of stages and their indications:

- Stage IA (G1, T1, M0): low grade within the bone, without metastasis
- Stage IB (G1, T2, M0): low grade outside the bone, without metastasis
- Stage IIA (G2, T1, M0): high grade within the bone, without metastasis
- Stage IIB (G2, T2, M0): high grade outside the bone, without metastasis
- Stage IIIA (G1 or G2, T1, M1): inside the bone, with metastasis
- Stage IIIB (G1 or G2, T2, M1): outside the bone, with metastasis

Physicians can employ several courses of treatment to remove chondrosarcomas. The most effective treatment is surgical removal. When performing the surgery, the doctor will remove the tumor and some healthy tissue or bone around it to ensure that the tumor does not recur near the original site. The physician may replace the removed bone with a metal device. In children, the metal device can be lengthened as the child grows, but this will require further surgeries. The fact that most chondrosarcomas tend to be low grade and slow-progressing makes this procedure one that does not necessitate entire limb removal except in extreme cases when the tumor is large.

Even individuals with low-grade chondrosarcoma that have undergone surgery experience a moderate risk of local recurrence. To combat recurrence, **chemotherapy** (the use of one or more cancer killing drugs) and

radiation therapy (the use of high energy rays) have also been used to complement surgery. Employing chemotherapy or radiation therapy individually (without surgery) is much less effective. In fact, chondrosarcomas are generally resistant to chemotherapy alone.

Low stage chondrosarcomas (Stages IA and IB) have greater one and five-year survival rates than the high stages (Stages IIIA and IIIB). High-grade tumors are more aggressive and highly metastatic than lower grade tumors, and therefore they have a lower survival rate. Not only is the grade of the tumor (the estimate of its aggressiveness) important in determining prognosis, but the age of the patient is also crucial. Generally, chondrosarcomas that occur in childhood and infancy have a higher mortality rate than those that occur in adults.

Metastases appear later in the development of chondrosarcomas. The lungs are the sites of primary metastasis. Once metastasis to the lungs has occurred, survival rate decreases.

Coping with cancer treatment

Chemotherapy often results in several side effects, depending on the drug used and the patient's individual tolerance. Patients may have to deal with nausea, vomiting, loss of appetite, and hair loss. Often, chemotherapy and radiation therapy are better handled if the patient is eating well. Nurses and dieticians can aid in choosing healthful foods to incorporate into the patient's diet.

If the chondrosarcoma necessitates limb **amputation**, the patient will need to learn how to cope with a prosthetic device. Both physical and vocational therapists can help the patient adjust and learn to use prosthetic devices to perform daily activities in new ways.

Clinical trials

Since chondrosarcomas are rare forms of cancer, there is still much to be learned. Clearly, surgery is the most effective treatment. New techniques in cryosurgery are being developed in various institutions across the country.

Chemotherapy trials have shown improved results with more intense regimens. Such drugs that are under study include **methotrexate**, **leucovorin**, **vincristine**, **bacillus Calmette Guérin**, **doxorubicin**, or a combination of two or three of these.

Patients should consult with their physicians or contact the American Cancer Society to learn what procedures are currently in **clinical trials**. In some cases, insurance companies will not cover clinical trial procedures. Patients should talk with their doctor and insurance company to determine which procedures are covered.

QUESTIONS TO ASK THE DOCTOR

- What diagnostic procedures are best for the location and type of tumor suspected?
- What treatments are best for the location and type of tumor suspected?
- What kinds of side effects will this course of treatment result?
- Are there support services available?
- What treatments are currently in clinical trials?
- What treatments will my health care insurance cover?

Prevention

Since little is known about what causes chondrosarcomas, there is also little known about how to prevent them. In general, the prevention of cancer can be assisted by avoiding known chemical carcinogens such as alpha-naphthylamine, carbon tetrachloride, and benzene. Another way to avoid developing cancer—especially bone cancer—is to minimize exposure to penetrating radiation such as x rays and radioactive elements. Medical x rays revolutionized the field of medicine and are used to detect and treat many diseases. In most cases, the benefits of medical x rays outweigh the risks.

Special concerns

Cancer treatments, especially surgical amputation, can take a physical and psychological toll on cancer patients and their families. To deal with the psychological impact, many different support groups and psychotherapists are available to help. Some therapists will consider amputation a post-traumatic stress disorder and treat it accordingly. Faith practices are also beneficial for cancer patients in dealing with their condition. Patients should discuss all options with their physician to determine what is available to them.

Once the cancer has been treated, patients should make sure to schedule follow-up appointments with their physicians. Physicians will want to monitor the patient for side effects or possible recurrence that may develop years after treatment.

See also Limb salvage; Tumor staging; Tumor grading.

Resources

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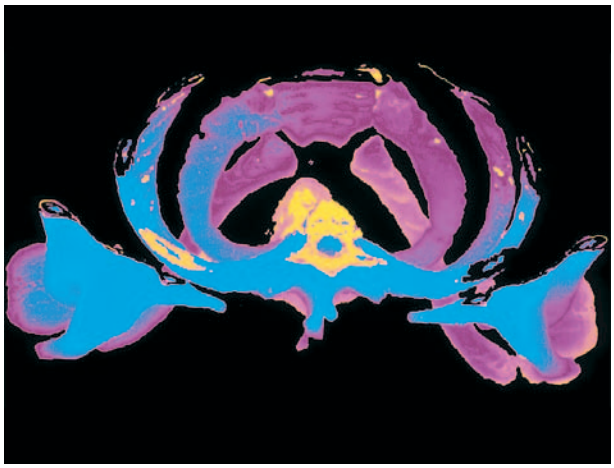
ORGANIZATIONS

American Cancer Society. <http://www.cancer.org>.

National Cancer Institute. <http://cancernet.nci.nih.gov>.

Sally C. McFarlane-Parrott



Colored 3-D computed tomography (CT) scan of the spine and ribcage of a male patient, showing cancer of the spine. The front of the body is at top, and at bottom left and right are the shoulder blades. The vertebral bone of the spine appears yellow and to the left of the vertebra is the cancerous tumor. *(Copyright Simon Fraser, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Chordoma

Definition

Chordomas are rare tumors of the central nervous system (brain and spinal cord).

Description

Chordomas are slow-growing tumors that invade bone and tissue surrounding the spinal column. They rarely spread to other parts of the body, but they can cause considerable damage or death because they destroy bone and soft tissue and often grow along the roots of nerves, putting pressure on the nerves and disrupting their function.

Chordomas appear at the base of the skull about 60% of the time and in the sacrum, located at the base of the spine, about 30% of the time. The other 10% of chordomas can occur anywhere else along the spinal column.

Demographics

Chordomas are very rare, accounting for between 1–4% of tumors of the brain and spinal column. Chordomas that occur at the base of the skull are most common in adults between 30 and 40 years of age. Those tumors that arise at the sacrum, located at the base of the spine, most commonly appear in older adults between the ages of 50 and 70. Chordomas are about twice as common in men as they are in women.

Causes and symptoms

During the fourth through sixth week of fetal development, a group of cells come together to form a structure called the notochord. The notochord defines the vertical mid-line of the body, and the spinal column develops around it. Normally, as development progresses, the notochord degenerates and disappears, except for small bits that become part of the disks between the spinal vertebrae. Chordomas are believed to develop from pieces of notochord that, for some reason, do not break down as they should. Over many years, these harmless bits of notochord transform and become malignant, forming chordomas.

Symptoms of chordoma depend on where the tumor is located. They are often vague and similar to symptoms of other tumors or even other conditions. Tumors located at the base of the skull may cause headaches, difficulty swallowing, or seizures depending on how much they have invaded the bones of the skull. Tumors located on the sacrum can cause general low back pain or difficulty with bowel and bladder control.

Diagnosis

Diagnosis has two parts: first, determining that the patient has a central nervous system tumor and where it is located, and second, determining what type of tumor it is. It is not easy to diagnose either of these.

A battery of tests is used to diagnose chordomas. A basic neurological examination tests the patient's reflexes,

KEY TERMS

Sacrum—The last five vertebrae (bones) of the spinal column, which are fused into a single mass commonly called the tail bone.

vision, hearing, senses of touch and smell, mental acuity, orientation, memory, and head and neck movements. If the results of the test indicate central nervous system dysfunction, the patient is usually referred to a neurologist (specialist in the central nervous system).

Several different scans are done to locate the tumor. Two of the most common are the **computed tomography** (CT or CAT) scan and **magnetic resonance imaging** (MRI). A CT scan uses x-ray images taken from many angles and computer reconstruction to show parts of the body in cross section. This helps to locate and estimate the size the tumor, and provides information on whether it can be surgically removed. MRI uses magnets and radio waves to create more detailed cross-sectional scans than computed tomography. There are many variations on these two scans that use dyes or radioactive materials to provide information about blood flow around the tumor and help determine whether the tumor can be surgically removed.

Treatment team

A neurosurgeon (a surgeon that specializes in the nervous system) will most likely lead the treatment team. A radiologist that specializes in nervous system radiology will interpret CT and MRI scans. Depending on the treatment plan, other members of the team may include a radiation oncologist (a specialist in **radiation therapy**), radiation technicians, and nurses with special training in assisting cancer patients.

Clinical staging, treatments, and prognosis

Staging of chordomas is less important in developing a treatment plan than it is for some other cancers, since chordomas rarely spread from their original location. If the tumor is in a location where it can safely be removed without damaging other nerves or structures, surgery is the preferred treatment.

But chordomas can be difficult to treat because the location of the tumor often makes it inoperable or impossible to remove completely. This is especially true of chordomas located at the base of the skull. When the tumor is inoperable, radiation therapy is the preferred treatment. Proton therapy, also called charged particle therapy, is a type of radiation treatment that spares the tissues around the tumor. For this reason, it is sometimes recommended for chordoma around the skull. One drawback of proton therapy is that the procedure is only offered at a few sites around in the United States. It is always appropriate to get a second opinion before agreeing to any treatment plan. Some insurers require second opinions before surgery.

The success of the treatment plan depends almost entirely on the location of the tumor. Chordomas can recur after either surgery or radiation therapy. They rarely spread (metastasize) to other parts of the body.

Alternative and complementary therapies

Alternative and complementary therapies range from herbal remedies, vitamin supplements, and special diets to spiritual practices, acupuncture, massage, and similar treatments. When these therapies are used in addition to conventional medicine, they are called complementary therapies. When they are used instead of conventional medicine, they are called alternative therapies.

No specific alternative therapies have been directed toward chordoma. However, good nutrition and activities, such as yoga, meditation, and massage, that reduce stress and promote a positive view of life have no unwanted side effects and appear to be beneficial. Alternative and experimental treatments are normally not covered by insurance.

Coping with cancer treatment

Cancer treatment, even when successful, has many unwanted side effects. Radiation therapy may cause **fatigue**, and **nausea and vomiting**. Bladder control and sexual function may be impaired after surgery on sacral chordomas. Mental functions may be impaired because of inoperable chordomas near the brain.

Discovering one has cancer is a traumatic event. Not only is one's health affected, one's whole life suddenly revolves around trips to the doctor for cancer treatment and adjusting to the side effects of these treatments. As this is a stressful time for both the cancer patient and family members, support groups and psychological counseling may be helpful. Many national organizations that support cancer education can provide information either in person or through on-line support and education groups.

Clinical trials

Chordoma is a rare tumor. In 2001, there were no **clinical trials** related to its diagnosis or treatment. However, the selection of clinical trials underway changes frequently. Current information on what clinical trials are available and where they are being held can be

QUESTIONS TO ASK THE DOCTOR

- What kinds of tests will you do?
- What will these tests tell you about my cancer?
- What are my treatment options?
- How will my treatment affect my daily life?
- Since chordoma is a rare tumor, how much experience do you have with it?
- Are there hospitals that specialize in the treatment of chordoma where I might receive treatment unavailable here?

found by entering the search term "chordoma" at the following websites:

- National Cancer Institute <http://cancertrials.nci.nih.gov> or (800) 4-CANCER.
- National Institutes of Health Clinical Trials <http://clinicaltrials.gov>.
- Center Watch: A Clinical Trials Listing <http://www.centerwatch.com>.

Prevention

There is no way to prevent chordoma. There appear to be no environmental factors that affect the development of this tumor.

Resources

ORGANIZATIONS

American Brain Tumor Association. 2720 River Road, Des Plaines, IL 60018. (847) 827-9910. Patient line (800) 886-2282. <http://www.abta.org>.

Tish Davidson, A.M.

Choriocarcinoma *see* **Gestational trophoblastic tumors**

Choroid plexus tumors

Definition

Choroid plexus tumors (CPTs) are rare abnormal growths on a part of the brain called the choroid plexus. The choroid plexus is the structure in the brain that produces the cerebrospinal fluid that coats the brain and spinal cord.

Description

There are two types of CPT: choroid plexus papilloma (CPP) and choroid plexus **carcinoma** (CPC). CPPs account for the majority of all CPTs.

A CPP is a benign, slow-growing, wart-like tumor that tends to grow on the surface of the choroid plexus. CPPs can spread by growing and by multiplying, just like warts, but they do not spread (metastasize) to organs that are not directly attached to the brain. A CPC is a malignant slow-growing tumor that tends to invade healthy brain tissue. CPCs can metastasize to distant parts of the body.

A primary brain tumor is a tumor that begins in the brain, as opposed to a secondary (or metastatic) brain tumor, which begins in another organ and metastasized to the brain. CPPs make up approximately 1% of primary brain tumors in adults and 3% of primary brain tumors in children.

Demographics

CPTs occur in approximately two of every one million people. CPTs can occur in people of any age, but greater than 70% of all CPTs occur in children younger than two years of age. When CPPs occur in children, they tend to be located in the uppermost portion of the spinal fluid pathway (the lateral ventricles). When they occur in adults, they tend to be located in the lower portion of the spinal fluid pathway in the brain (the fourth ventricle). CPCs occur almost exclusively in children, most under the age of two years, and are almost always located in the lateral ventricles.

CPTs occur with equal frequency in members of all races and ethnic groups. There does not appear to be any relationship of CPTs to any geographic region. Males and females are affected in equal numbers by CPTs.

Causes and symptoms

The cause, or causes, of CPTs are not known. In early 2001, ongoing investigations attempted to determine if environmental factors, genetic factors, viruses, or other factors caused primary brain tumors. Primary brain tumors are not contagious.

The symptoms of CPTs are the result of increased pressure in the fluid within the skull (intracranial hypertension). These symptoms include:

- nausea
- vomiting

KEY TERMS

Choroid plexus—Tissues of the brain that produce the fluid that coats the brain and spinal cord.

Choroid plexus carcinoma (CPC)—A malignant tumor of the choroid plexus that often invades the underlying brain tissues and can spread to other parts of the body.

Choroid plexus papilloma (CPP)—A benign tumor of the choroid plexus that does not invade the underlying brain tissues and does not spread to other parts of the body.

Intracranial hypertension—A higher than normal pressure of the fluid in the skull.

Spinal fluid shunt—A small tube that is surgically implanted to allow excess spinal fluid to drain directly into the abdominal cavity.

- irritability
- headache
- vision disturbances
- enlargement of the head
- seizures

CPCs may also be accompanied by:

- bleeding (hemorrhage) at the site of the tumor
- weakness or paralysis on the side of the body opposite to the side of the brain where the tumor is located.

Diagnosis

The diagnosis of CPTs begins in the doctor's office. After taking a complete medical history, the doctor will perform a basic neurological examination. This examination involves:

- testing eye reflexes, eye movement, and pupil reactions
- testing hearing with a tuning fork or ticking watch
- reflex tests with a rubber hammer
- balance and coordination tests
- pin-prick and cotton ball tests for sense of touch
- sense of smell tests with various odors
- facial muscle tests: smiling, frowning, etc.
- tongue movement and gag reflex tests
- head movement tests
- mental status tests: asking what year it is, who the president is, etc.
- abstract thinking tests: asking for the meaning of a common saying, such as "every cloud has a silver lining."
- memory tests: asking to have a list of objects repeated, asking for details of what a patient ate for dinner last night, etc.

If the doctor suspects a brain tumor may be present, further diagnostic tests will be ordered. These tests are performed by a neurological specialist. Imaging tests that may be ordered include:

- **computed tomography** (CT scan)
- **magnetic resonance imaging** (MRI)

Other tests may include:

- a **lumbar puncture**, or spinal tap, to examine the cerebrospinal fluid
- an electroencephalogram (EEG), which measures the electrical activity of the brain

Treatment team

Treatment of any primary brain tumor, including the CPTs, is different from treating tumors in other parts of the body. Brain surgery requires much more precision than most other surgeries. Also, many medicinal drugs cannot cross the blood-brain barrier. Therefore, the therapies that are used to treat CPTs, and the side effects of these therapies, are quite complex.

The most up-to-date treatment opportunities are available from experienced, multidisciplinary medical professional teams made up of doctors, nurses, and technologists who specialize in cancer (oncology), neurology, medical imaging, drug or **radiation therapy**, and anesthesiology.

Clinical staging, treatments, and prognosis

CPTs and other primary brain tumors are diagnosed, or staged, in grades of severity from I to IV. Grade I tumors have cells that are not malignant and are nearly normal in appearance. Grade II tumors have cells that appear to be slightly abnormal. Grade III tumors have cells that are malignant and clearly abnormal. Grade IV, the most severe type of brain tumor, contains fast-spreading and abnormal cells. The standard treatment for all grades of CPTs is surgery to completely remove the tumor or tumors. This surgery is generally aided by an image guidance system that allows the surgeon to determine the most efficient route to take to the location of the tumor.

Approximately one-half of CPT patients gain relief of the increased intracranial pressure after complete

QUESTIONS TO ASK THE DOCTOR

- Which type of CPT do I have?
- Is my tumor operable?
- What is the likelihood of my type of CPT coming back?
- How often should I seek follow-up examinations?

removal of their tumors. The other half require a spinal fluid shunt to allow drainage of the excess fluid.

In some instances of CPC, the tumor is inoperable. Patients with inoperable CPCs are generally treated with radiation therapies. CPPs are highly resistant to radiation treatment, so these therapies are not used for CPPs.

As of 1999, 8.6% of patients who had surgery to remove CPTs died within five years of the surgery. One-half of these patients (4.3%) died during the surgery itself.

Alternative and complementary therapies

There are no effective alternative treatments for CPTs other than surgery and radiation therapies in the case of inoperable CPCs.

Coping with cancer treatment

Most patients who undergo brain surgery to remove their tumors can resume their normal activities within a few days of the operation.

Clinical trials

There were 19 **clinical trials** underway in early 2001 aimed at the treatment of CPTs. More information on these trials, including contact information, may be found by conducting a clinical trial search at the Web site of the National Cancer Institute, CancerNet (http://cancernet.nci.nih.gov/trialsrch.shtml).

Prevention

Because the causes of CPTs are not known, there are no known preventions.

Special concerns

Repeat surgery may be necessary for CPTs because these tumors sometimes redevelop. Careful monitoring by the medical team will be required.

Resources

ORGANIZATIONS

The Brain Tumor Society. 124 Watertown Street, Suite 3-H. Watertown, MA 02472. Telephone (617)924-9997. Fax (617)924-9998. <http://www.tbts.org>.

National Brain Tumor Foundation. 785 Market Street, Suite 1600, San Francisco, CA 94103. Telephone (415)284-0208. <http://www.braintumor.org>.

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Paul A. Johnson, Ed.M.

Chromic phosphate P32 *see* **Radiopharmaceuticals**

Chromosome rearrangements

Definition

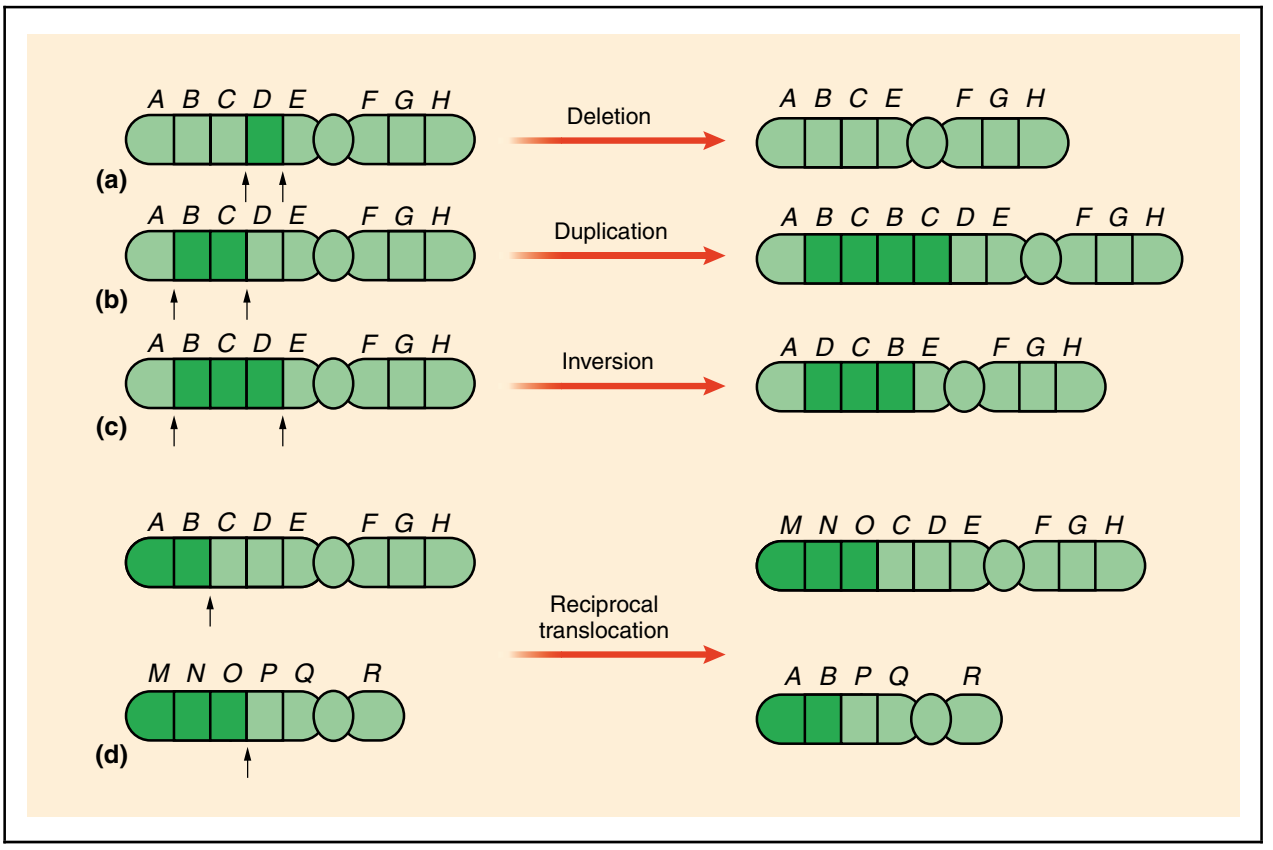
A chromosome rearrangement is a structural change in a chromosome such as a deletion, translocation, inversion, or gene amplification. Chromosome rearrangements can contribute to the transformation of a normal cell into a cancerous cell and are therefore found in many cancer cells.

Description

Chromosomes and genes

A chromosome is a microscopic structure which is composed of proteins and DNA and is found in every cell of the body. Each cell of the body, except for the egg and the sperm cells, contains 23 pairs of chromosomes and 46 chromosomes in total. All cells of the body except for the egg and sperm cells are called the somatic cells. The egg and sperm cells each contain 23 chromosomes. Both males and females have 22 pairs of chromosomes, called the autosomes, that are numbered one to twenty-two in order of decreasing size. The final pair of chromosomes, called the sex chromosomes, determine the sex of the individual. Women possess two identical chromosomes called the X chromosomes while men possess one X chromosome and one Y chromosome.

Each type of chromosome contains different genes that are found at specific locations along the



Four kinds of chromosome rearrangements. Arrows indicate where chromosomes break, and dark green indicates the genes affected. (a)A deletion removes a chromosome segment. (b)Duplication repeats a segment. (c)Inversion reverses the order of a segment. (d)A translocation moves a segment from one chromosome to another. Each chromosome contains genes found at specific locations along the chromosome, and each gene contains the instructions for the production of a protein. If a gene produces proteins involved in controlling the cell's growth cycle, and this gene is affected by a chromosome rearrangement, uncontrolled cell growth (cancer) could result. *(Illustration by Argosy Publishing.)*

chromosome. Men and women possess two of each type of autosomal gene since they inherit one of each type from each parent. Each gene contains the instructions for the production of a particular protein. The proteins produced by genes have many functions and work together to create the traits of the human body, such as hair and eye color, and are involved in controlling the body's basic functions. Some genes produce proteins that are involved in controlling the growth cycle of the cell and are therefore involved in preventing the development of cancer.

Types of chromosome rearrangements

Sometimes a spontaneous break or breaks occur in a chromosome or chromosomes in a particular cell and can result in a deletion, inversion, or translocation. If the break or breaks result in the loss of a piece of chromosome, it is called a deletion. An inversion results when a segment of chromosome breaks off, is reversed (inverted), and is reinserted into its original location. When a piece of one chromosome is exchanged with a piece from another chromosome it is called a translocation.

Sometimes a small segment of chromosome is amplified, which results in the presence of multiple copies of that section of the chromosome. In most cases the segment of the chromosome that is duplicated contains only one gene, although it is possible for more than one gene to be amplified. Sometimes amplified genes form a separate and unique chromosome and sometimes they are located within an otherwise normal chromosome.

Chromosome rearrangements and cancer

A chromosome rearrangement can delete or disrupt the functioning of genes that are located on the chromosomal pieces involved. Chromosome rearrangements that delete or disrupt genes that regulate the cell cycle can contribute to the transformation of a normal cell into

a cancerous cell. That is why chromosomal rearrangements are found in many cancers.

THE TRANSFORMATION OF A NORMAL CELL INTO A CANCEROUS CELL The process by which a normal cell is transformed into a cancerous cell is a complex, multi-step process involving a breakdown in the normal cell cycle. Normally a somatic cell goes through a growth cycle during which it produces new cells. The process of cell division is necessary for the growth of tissues and organs of the body and for the replacement of damaged cells.

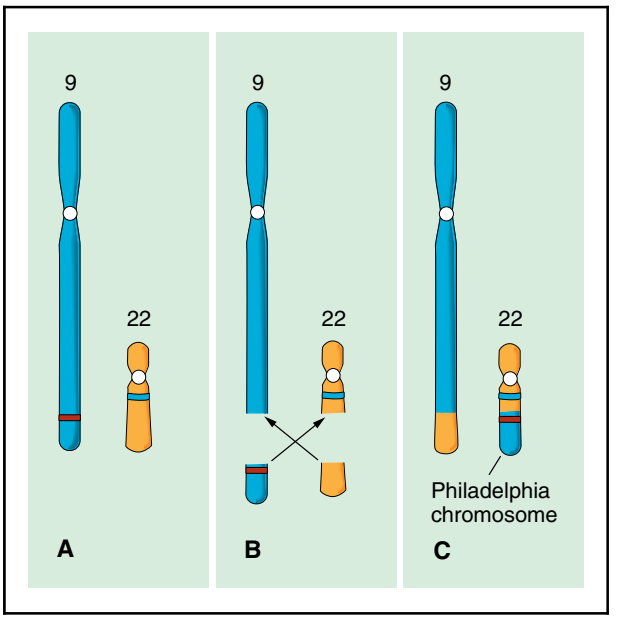
Cell division is tightly regulated by genes. Normal cells have a limited lifespan and only go through the cell cycle a certain number of times. Genes regulate the cell cycle by producing regulatory proteins. Different types of regulatory proteins regulate cell growth and division in different types of cells. For example, a skin cell may be regulated by a different combination of proteins than a breast cell or a liver cell.

A cell that loses control of its cell cycle and replicates out of control is called a cancer cell. Cancer cells undergo many cell divisions, often at a quicker rate than normal cells, and do not have a limited lifespan. They also have loss of apoptosis, or cell death, which is characteristic of a normal cell. This allows them to eventually overwhelm the body with a large number of abnormal cells and hurt the functioning of the normal cells.

A cell becomes cancerous only after changes or deletions occur in a number of genes that are involved in the regulation of its cell cycle. However, a change or deletion of one regulatory gene can result in the change or deletion of other regulatory genes.

Proto-oncogenes and tumor-suppressor genes are the two most common types of genes involved in regulating the cell cycle. We inherit two of each type of proto-oncogene and two of each type of tumor-suppressor gene. Tumor-suppressor genes produce proteins that are involved in helping to prevent uncontrolled cell growth and division. Only one normal copy of a tumor-suppressor gene needs to be present to maintain its normal role in the regulation of the cell cycle. If both copies of a tumor-suppressor gene are changed, however, then not enough normal tumor-suppressor protein will be produced and the cell is more likely to become cancerous.

Proto-oncogenes produce proteins that are largely involved in stimulating the growth and division of cells in a controlled manner. A change in a proto-oncogene can convert it into an oncogene. An oncogene produces an abnormal protein, which is involved in stimulating uncontrolled cell growth. Only one proto-oncogene of a pair needs to be changed into an oncogene for it to promote the transformation of a normal cell into a cancerous cell.



A. Normal chromosomes. B. Breakage occurs near a proto-oncogene on chromosome 9. C. Translocation chromosomes. This translocation, called the Philadelphia chromosome, can result in chronic myelocytic leukemia. *(Illustration by Argosy Publishing.)*

A chromosome rearrangement involving a tumor-suppressor gene or proto-oncogene can contribute to the transformation of a normal cell into a cancerous cell. Certain types of chromosome rearrangements are found more commonly in cancers of certain types of cells. This is because these chromosome rearrangements involve genes that regulate the cell cycle in those specific cells. More than one chromosome rearrangement is usually present in a particular cancer cell since it is necessary for more than one regulatory gene to be altered during the transformation of a normal cell into a cancerous cell. Different types of chromosome rearrangements contribute to the formation of cancer cells in different ways. Researchers don't always know how a chromosome rearrangement contributes to the development of cancer.

How specific types of rearrangements contribute to the development of cancer

Deletions

A deletion of a piece of chromosome that contains a tumor suppressor gene can contribute to the transformation of a normal cell into a cancerous cell. If both copies of a tumor suppressor gene are deleted or

KEY TERMS

Chromosome—A microscopic structure, made of a complex of proteins and DNA, that is found within each cell of the body.

Deletion—A piece missing from a chromosome.

Gene—A building block of inheritance, made up of a compound called DNA (deoxyribonucleic acid) and containing the instructions for the production of a particular protein. Each gene is found on a specific location on a chromosome.

Gene amplification—When multiple copies of a small segment of chromosome containing one or more genes are present as a separate chromosome or as part of an otherwise normal chromosome.

Inversion—A piece of a chromosome that was removed from the chromosome, inverted, and reinserted into the same location on the chromosome.

Leukemia—Cancer of the blood-forming organs which results in an overproduction of white blood cells.

Lymphoma—Cancer involving cells of the immune system.

Oncogene—A changed proto-oncogene that promotes uncontrolled cell division and growth.

Protein—A substance produced by a gene that is involved in creating the traits of the human body such as hair and eye color or is involved in controlling the basic functions of the human body.

Proto-oncogene—A gene involved in stimulating the normal growth and division of cells in a controlled manner.

Somatic cells—All the cells of the body except for the egg and sperm cells.

Translocation—An exchange of a piece of one chromosome with a piece from another chromosome.

Tumor-suppressor gene—Gene involved in controlling normal cell growth and preventing cancer.

changed then little or no tumor suppressor protein is produced. This in turn can impact the regulation of the cell cycle and contribute to the transformation of the normal cell.

A deletion of a segment of chromosome 13, for example, can result in the loss of a tumor-suppressor gene that helps to prevent an eye cancer called **retinoblastoma**. If both retinoblastoma tumor-suppressor genes are deleted or changed in one of the cells of the eye then that cell can become cancerous.

Translocations

A translocation involving a proto-oncogene can result in its conversion into an oncogene which can contribute to the development of cancer. A translocation involving a proto-oncogene results in the transfer of the proto-oncogene from its normal location on a chromosome to a different location on another chromosome. Sometimes this results in the transfer of a proto-oncogene next to an activating gene. This activating gene abnormally activates the proto-oncogene and converts it into an oncogene. When this oncogene is present in a cell, it contributes to uncontrolled cell growth and the development of cancer.

For example, the translocation of the c-myc proto-oncogene from its normal location on chromosome eight to a location on chromosome 14 results in the abnormal activation of c-myc. This type of translocation is involved in the development of a type of cancer called **Burkitt's lymphoma**. The translocated c-myc proto-oncogene is found in the cancer cells of approximately 85% of people with Burkitt's lymphoma.

A translocation involving a proto-oncogene can also result in the fusion of the proto-oncogene with another gene. The resulting fused gene is an oncogene that produces an unregulated protein which stimulates uncontrolled cell growth. One example is the Philadelphia chromosome translocation, found in the leukemia cells of greater than 95% of patients with a chronic form of leukemia. The Philadelphia chromosome translocation results in the fusion of the c-abl proto-oncogene, normally found on chromosome nine, to the bcr gene that is found on chromosome 22. The fused gene produces an abnormal protein that is involved in the formation of cancer cells.

Inversions

An inversion, like a translocation, can result in the creation of an oncogene through either the activation of a proto-oncogene or the creation of a fusion gene. An inversion involving a proto-oncogene results in the movement of the gene to another location on the same chromosome. For example, an inversion of chromosome ten can move a proto-oncogene called RET and cause it to fuse with a gene called ELEI or a gene called H4. The fusion of RET with either of these genes creates an oncogene. When the RET oncogene is present in a thyroid cell it promotes the transformation of that cell into a cancerous cell.

Gene amplification

Gene amplification can also contribute to the development of cancer. Amplification of a segment of chromosome that contains a proto-oncogene can result in the formation of many copies of a proto-oncogene. Each copy of the proto-oncogene produces protein that is involved in stimulating cell growth. This can result in a significant increase in the amount of protein produced, which can promote uncontrolled cell growth. Multiple copies of proto-oncogenes are found in many tumors.

See also Cancer genetics.

Resources

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Lisa Andres, M.S., CGC

Chronic leukemia

Definition

A slowly progressing cancer that starts in blood-forming cells of the bone marrow. Leukemias are the result of an abnormal development of leukocytes (white blood cells) and their precursors. Leukemia cells look different than normal cells and do not function properly.

Description

There are four main types of leukemia, which can be further divided into subtypes. When classifying the type of leukemia, the first steps are to determine whether the cancer is lymphocytic or myelogenous (cancer can occur in either the lymphoid or myeloid white blood cells) and whether it is acute or chronic (rapidly or slowly progressing).

Chronic leukemia cells live much longer than normal white blood cells, resulting in an accumulation of too many mature granulocytes or lymphocytes. Chronic leukemia progresses slowly but can develop into an acute form. Major types include **chronic lymphocytic leukemia** (CLL) and **chronic myelocytic leukemia** (CML).

Lata Cherath, Ph.D.
Bob Kirsch

Chronic lymphocytic leukemia

Definition

Chronic lymphocytic leukemia (CLL) is a cancer of white blood cells. In CLL, mature white blood cells of certain types, called lymphocytes, function abnormally and cause disease.

Description

Chronic leukemia is a cancer that starts in the blood cells made in the bone marrow. The bone marrow is the spongy tissue found in the large bones of the body. The bone marrow makes precursor cells called "blasts" or "stem cells" that mature into different types of blood cells. Unlike acute leukemias, in which the process of maturation of the blast cells is interrupted, in chronic leukemias, most of the cells do mature and only a few remain as immature cells. However, even though the cells appear normal, they do not function as normal cells.

The different types of cells produced in the bone marrow are red blood cells (RBCs), which carry oxygen and other materials to all tissues of the body, and white blood cells (WBCs), which fight infection. Platelets play a part in the clotting of the blood. The white blood cells can be further subdivided into three main types: the granulocytes, monocytes, and the lymphocytes.

The granulocytes, as their name suggests, contain granules (particles). These granules contain special proteins (enzymes) and several other substances that can break down chemicals and destroy microorganisms such as bacteria. Monocytes are the second type of white blood cell. They also are important in defending the body against pathogens.

The lymphocytes form the third type of white blood cell. There are two main types of lymphocytes: T lymphocytes and B lymphocytes. They have different

functions within the immune system. The B cells protect the body by making "antibodies." Antibodies are proteins that can attach to the surfaces of bacteria and viruses. The occurrence of this attachment sends signals to many other cell types to travel through the blood and destroy the antibody-coated organism. The T cell protects the body against viruses. When a virus enters a cell, it produces certain proteins that are projected onto the surface of the infected cell. T cells recognize these proteins and produce certain chemicals (cytokines) capable of destroying the virus-infected cells. In addition, T cells destroy some types of cancer cells.

Chronic leukemias develop very gradually. The abnormal lymphocytes multiply slowly, and in a poorly regulated manner. These lymphocytes live much longer than normal lymphocytes and, thus, their numbers build up in the body. In CLL, lymphocytes accumulate. The enlarged lymphocyte population congregates in the blood, bone marrow, lymph nodes, spleen, and liver. The two types of chronic leukemias can be easily distinguished under the microscope. Chronic lymphocytic leukemia (CLL) involves the T or B lymphocytes. B-cell abnormalities are more common than T-cell abnormalities. T cells are affected in only 5% of the patients.

Demographics

Ninety percent of CLL cases are seen in people who are 50 years or older, with the average age at diagnosis being 65. Rarely is CLL diagnosed in a patient who is less than 35 years of age. The incidence of the disease increases with age. It is almost never seen in children. According to the estimates of the American Cancer Society (ACS), approximately 8,100 new cases of CLL were diagnosed in 2000, 4,600 in men and 3,500 in women.

CLL affects both sexes. Among patients younger than 65, the disease is slightly more common in men. However, among patients older than 75 years of age, CLL appears almost equally in men and women. Within the United States, CLL affects African-Americans as frequently as it does Caucasians. However, CLL appears more frequently among Americans than among people living in Asia, Latin America, and Africa.

In the United States and Europe, CLL accounts for more than one-quarter of all diagnosed leukemias. Over the past 50 years, the rate at which CLL has been appearing has increased significantly. However, many doctors think that this increase is not necessarily due to the disease actually being more common than in the past, but instead due to the fact that the disease is now more likely to be diagnosed when it does appear. Fifty years ago, only one out of ten CLL patients was diagnosed during the early stages of the disease. Now, half of all CLL patients are diagnosed during this early stage.

Causes and symptoms

The cause of CLL is unknown. It is certain, however, that CLL is linked to genetic abnormalities and environmental factors. For example, close family members of patients with CLL are twice as likely to seven times as likely to be diagnosed with CLL as people in the general population. For another example, exposure to certain chemicals used in farming and other agricultural occupations may increase the risk that a person will develop CLL. In contrast, CLL is not associated with exposure to radiation known to cause other cancers. As of 2001, doctors were unsure whether people who have had certain virus infections are more likely to develop CLL than are people in the general population. If there does turn out to be such an association, it would not be with all viruses but with two human retroviruses (HTLV-I and HTLV-II) or with **Epstein-Barr virus** (EBV).

The symptoms of CLL are generally vague and nonspecific. One out of five patients with CLL has no symptoms at all, and the disease is discovered only through a routine blood test. A patient may experience all or some of the following symptoms:

- chronic **fatigue**
- weakness
- a general feeling of malaise or of things being not quite right
- swollen lymph nodes
- an enlarged spleen, which could make the patient complain of abdominal fullness
- a general feeling of ill health
- **fever**
- frequent bacterial or viral infections.
- unusually severe response to insect bites
- **night sweats**
- **weight loss** not due to dieting or exercise

Diagnosis

There is no **screening test** for CLL. If the doctor has reason to suspect leukemia, he or she will conduct a very thorough physical examination to look for enlarged lymph nodes in the neck, underarm, and pelvic region. In addition, the doctor will look to see whether the liver and spleen are enlarged. Urine and blood tests may be ordered to check for microscopic amounts of blood in the urine and to obtain a

complete differential blood count. This count will give the numbers and percentages of the different cells found in the blood. An abnormal blood test might suggest leukemia. Some authorities state that CLL may be diagnosed if the number of lymphocytes in the blood exceeds a certain level.

The doctor may perform a **bone marrow aspiration and biopsy** to confirm the diagnosis of leukemia. During the bone marrow biopsy, a cylindrical piece of bone and marrow is removed. The tissue is generally taken out of the hipbone. These samples are sent to the laboratory for examination. In many CLL patients, more than one-fourth of the bone marrow is made up of mature lymphocytes. In addition to diagnosis, bone marrow biopsy is also conducted during the treatment phase of the disease to see if the leukemia is responding to therapy.

Some CLL patients have a condition called hypogammaglobulinemia. Immunoglobulins are normal parts of the body's immune system, the system used to fight off infection. Patients with hypogammaglobulinemia have very low levels of all of the various types of immunoglobulins.

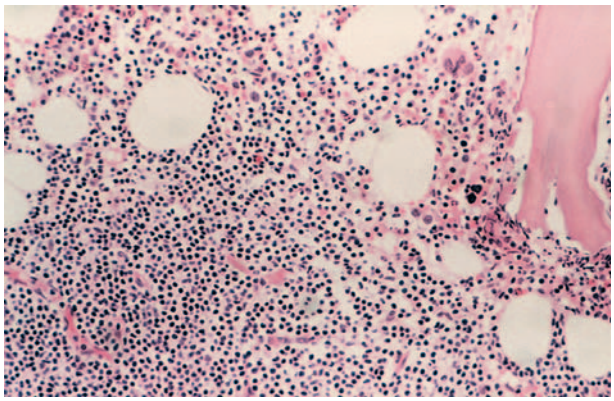
The doctor may also conduct immunophenotyping. This involves taking a sample of the blood and looking at what types of cells of the immune system are being affected by the CLL. Approximately 19 out of 20 CLL patients have the B-cell type of CLL. Far more rare is the T-cell type of CLL. In addition, the doctor may look for abnormalities in the chromosomes of the affected cells. Chromosomes are a unit of genetic material within cells. Patients exhibiting no chromosomal abnormalities have a better prognosis than those who do have such abnormalities. If the abnormalities become more complex over time, the patient's prognosis may worsen.

Standard imaging tests such as x rays, **computed tomography** scans (CT scans), and **magnetic resonance imaging** (MRI) may be used to check whether the leukemic cells have invaded other organs of the body, such as the bones, chest, kidneys, abdomen, or brain.

Clinical staging, treatments, and prognosis

Staging

Usually one of two systems are used to stage CLL. One of these is the Binet system and the other the Rai system. According to the Rai system, patients at low risk have no enlargement of lymph nodes, spleen or liver. The occurrence of these marks entry into the intermediate stage, according to Rai. High risk patients have, in addition, **anemia** and a significant decrease in the number of blood platelets in their blood. Blood platelets help blood to clot. According to the Binet system, a patient's stage depends upon how much hemoglobin (part of red blood cells that carry oxygen) and how many platelets are in the blood, as well as how many other areas the disease has affected. According to both systems, patients at low risk usually survive more than ten years. Patients at intermediate risk usually survive about six years. Patients at high risk usually survive about 2 years. Other factors with important implications for prognosis include the pattern at which bone marrow is being affected by the CLL and the amount of time it takes for the number of lymphocytes to double.



Bone marrow in chronic lymphocytic leukemia. In this disease, bone marrow is replaced by small, mature lymphoid cells. *(Photo Researchers, Inc. Reproduced by permission.)*

Treatment

Because the long-term prognosis for many patients with CLL is excellent, many patients receive no treatment at all at first. Many patients go for years before developing aggressive disease that requires treatment. Treatment for early stage CLL should be started only when one of the following conditions appears:

- Symptoms of the disease are growing worse, for example, there is a greater degree of fever, weight loss, night sweats, and so forth.
- The spleen is enlarging or enlargement of the spleen has become painful.
- Disease of the lymph nodes has become more severe.
- The condition of the bone marrow has deteriorated and there is anemia and a marked reduction in the number of blood platelets.
- There is anemia or reduction in the number of blood platelets for reasons not specifically related to the condition of the bone marrow.
- The population of lymphocytes is rapidly growing.
- The patient is experiencing numerous infections caused by bacteria.

Therapy for CLL usually starts with **chemotherapy**. Depending on the stage of the disease, single or multiple drugs may be given. Drugs commonly prescribed include **fludarabine**, **cladribine**, **chlorambucil** and **cyclophosphamide**. Studies have also provided evidence that a combination of fludarabine and cyclophosphamide is effective. However, this combination has not yet been evaluated over periods of ten years or more. Another combination now being studied involves fludarabine and **mitoxantrone** (Novantrone). Yet another involves fludarabine and anthracyclines. Low-dose **radiation therapy** may be given to the whole body, or it may be used to alleviate the symptoms and discomfort due to an enlarged spleen and lymph nodes. The spleen may be removed in a procedure called a **splenectomy**.

Bone marrow transplantation (BMT) has produced some positive outcomes in patients with CLL, although it has not been the subject of sufficient systematic study to permit doctors to know how effective it is. In BMT, the patient's diseased bone marrow is replaced with healthy marrow. There are two ways of performing a bone marrow transplant. In an allogeneic bone marrow transplant, healthy marrow is taken from another person (donor) whose tissue is either the same or very closely resembles the patient's tissues. The donor may be a twin, a sibling, or a person who is not related at all. First, the patient's bone marrow is destroyed with very high doses of chemotherapy and radiation therapy. To replace the destroyed marrow, healthy marrow from the donor is given to the patient through a needle in the vein.

In the second type of bone marrow transplant, called an autologous bone marrow transplant, some of the patient's own marrow is taken out and treated with a combination of anticancer drugs to kill all the abnormal cells. This marrow is then frozen to save it. The marrow remaining in the patient's body is then destroyed with high-dose chemotherapy and radiation therapy. Following that, the patient's own frozen marrow is thawed and given back to the patient through a needle in the vein. The use of this mode of bone marrow transplant for the treatment of CLL is currently being investigated in **clinical trials**.

Allogeneic BMT has been successfully used with younger patients with CLL who have not responded positively to chemotherapy. Autologous BMT has produced some positive results in older CLL patients. However, BMT is generally not considered an option in treating most patients with CLL because they are too old to be considered good candidates for the procedure.

Other CLL therapies that are being investigated include monoclonal antibody-targeted therapy and **interferons**. **Monoclonal antibodies** (MoAbs) are laboratory-manufactured chemicals that closely resemble parts of the body's natural immune system. Studies of MoAbs-targeted therapies have shown some positive results in CLL, although definitive studies have not been performed at the time of this writing in 2001. Interferon is a chemical normally made in the cells of the body. It helps protect the body against viruses and also seems to have some effect against certain cancers. The interferon used as medicine is a laboratory-manufactured copy of the interferon produced by the body. As of this writing in 2001, interferon therapy has produced some response in CLL patients. However, interferon therapy has not as yet been shown to be associated with prolongation of remission.

Radiation therapy is very effective for approximately one in three of those CLL patients for whom it is considered appropriate.

Because leukemia cells can spread to all the organs via the blood stream and the lymph vessels, surgery is not considered an option for treating leukemias.

Treatment of CLL and its complications

During therapy for CLL, complications frequently appear. Many patients develop infectious illnesses. Sometimes, two or more infectious diseases attack a patient at the same time. These infections should be treated with great care. Most people whose death has been directly attributed to CLL have actually died from bacterial infections. The patient should be involved in identifying symptoms of infection and reporting these to the doctor without delay. Doing so may save the patient's life.

Many patients develop anemia, which is treated with the drug prednisone. Patients who do not respond to prednisone therapy may have their spleen removed and may receive therapy with immunoglobulin, a component of the blood.

Treatment after transformation of CLL

Between three and ten out of every hundred patients with CLL experiences transformation of the disease into large-cell lymphoma (LCL). When this happens it is called Richter's transformation. Its occurrence is often marked by fever, weight loss, and night sweats. Treatments for LCL are being studied, although outcomes have not been very good. Very infrequently, CLL may transform into another disease, called prolymphocytic leukemia. Attempts to develop adequate therapies for this disease are ongoing.

Prognosis

For many CLL patients, the prognosis is excellent. Using the Binet and Rai staging systems, patients at low risk usually survive more than ten years. Patients at intermediate risk usually survive about six

years. Patients at high risk usually survive about two years. The average patient survives approximately nine years following diagnosis. Factors with important implications for prognosis that are not included in the Binet or Rai systems are the pattern at which bone marrow is being affected by the CLL and the amount of time it takes for the number of lymphocytes in the blood to double. It is uncertain whether BMT may prolong the lifespan of CLL patients. Many of the chemotherapy agents used to treat disease do effectively control the leukemia and its effects but, as yet, the more established chemotherapy agents have not been shown to increase the life span of patients.

Coping with cancer treatment

Since many CLL patients die from infection, it is essential that patient be very alert to the signs of infection. If patients perform this role and seek medical attention as soon as symptoms of infection appear, then treatment can be started early. This may save a life.

It is very difficult for some patients to be not only informed that they have leukemia but then to also be told that they do not need treatment. This may be very confusing, unless the patient realizes that treatment may be necessary at some future time and that starting therapies too soon may be counterproductive.

Because nutritional alteration, weight loss, and psychosocial problems may accompany CLL, it may be prudent for patients to consult with a registered dietitian.

Cancer patients need supportive care to help them come through the treatment period with physical and emotional strength in tact. Many patients experience feelings of **depression**, anxiety, and fatigue, and many experience **nausea and vomiting** during treatment. Studies have shown that these can be managed effectively if discussed with the attending physician.

Prevention

Although some cancers are related to known risk factors, such as smoking, in leukemias, there are no known risk factors. Therefore, at the present time, there is no way known to prevent the leukemias from developing. Everyone should undergo periodic medical checkups.

KEY TERMS

Antibodies—Proteins made by the B lymphocytes in response to the presence of infectious agents, such as bacteria or viruses, in the body.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Chemotherapy—Treatment with drugs that act against cancer.

Chromosome — Part of the cell that carries genetic material.

Cytokines—Chemicals made by the cells that act on other cells to stimulate or inhibit their function. Cytokines that stimulate growth are called "growth factors."

Immunotherapy—Treatment of cancer by stimulating the body's immune defense system.

Maturation—The process by which stem cells transform from immature cells without a specific function into a particular type of blood cell with defined functions.

Radiation therapy—Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Remission—A disappearance of a disease as a result of treatment. Complete remission means that all disease is gone. Partial remission means that the disease is significantly improved by treatment, but residual traces of the disease are still present.

Resources

BOOKS

Braunwald, Eugene, et al. *Harrison's Principles of Internal Medicine* . 15th ed. New York: McGraw-Hill, 2001.

Herfindal, Eric T., Dick R. Gourley. *Textbook of Therapeutics: Drug and Disease Management*. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2000.

Humes, H. David, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2000.

Pazdur, Richard, et al. *Cancer Management: A Multidisciplinary Approach: Medical, Surgical, & Radiation Oncology*. 4th ed. Melville, NY: PRR, 2000.

PERIODICALS

Mauro, F. R., et al. "Clinical characteristics and outcome of young chronic lymphocytic leukemia patients: A single institution study of 204 cases." *Blood* 1999; 94: 448-454.

ORGANIZATIONS

The American Cancer Society publishes useful texts, such as *Adult Chronic Leukemia - Overview, Leukemia - Adult Chronic: Treatment, Leukemia - Adult Chronic: Detection and Symptoms, Leukemia: Adult Chronic FAQ [Frequently Asked Questions]*, and *Leukemia - Adult Chronic: Prevention & Risk*. Call 1-800-ACS-2345 or on the Internet at <www.cancer.org/>

The Leukemia & Lymphoma Society (Formerly Leukemia Society of America) publishes useful texts available through the Internet or by mail, including *Chronic Lymphocytic Leukemia (CLL), Making Intelligent Choices About Therapy, Understanding Blood Counts, Patient Aid Program, Family Support Group,* and *Information Resource Center*. Call 1-800-955-4572 or visit on the Internet at <www.leukemia-lymphoma.org/>.

The National Cancer Institute publishes useful texts available through the internet or by mail, and answers questions by telephone. Some titles include: *What You Need to Know about Leukemia* and *PDQ - Treatment - Patients: Chronic Lymphocytic Leukemia*. Call 1-800-4CANCER or visit on the Internet at <www.nci.nih.gov/>.

National Coalition for Cancer Survivorship. 1010 Wayne Avenue, 7th Floor, Silver Spring, MD 20910-5600. Telephone: (301) 650-9127 and (877) NCCS-YES [877-622-7937). Web site: <www.cansearch.org>.

Lata Cherath, Ph.D.
Bob Kirsch

Chronic myelocytic leukemia

Definition

Chronic myelocytic leukemia (CML) is a cancer of white blood cells in which too many white blood cells are made in the bone marrow. Chronic myelogenous leukemia and chronic myeloid leukemia are other names for CML and refer to the identical disease. Depending on the type of white blood cell that is involved, chronic leukemia can be classified as **chronic lymphocytic leukemia** or chronic myelocytic leukemia. In chronic myelocytic leukemia, there is an increased proliferation of white blood cells called granulocytes.

Description

Chronic leukemia is a cancer that starts in the blood cells made in the bone marrow. The bone marrow is the spongy tissue found in the large bones of the body. The bone marrow makes precursor cells called "blasts" or "stem cells" that mature into different types of blood cells. Unlike acute leukemias, in which the process of maturation of the blast cells is interrupted, in chronic leukemias, the cells do mature and only a few remain as immature cells. However, even though the cells appear normal, they do not function as normal cells.

The different types of cells produced in the bone marrow are red blood cells (RBCs), which carry oxygen and other materials to all tissues of the body; white blood cells (WBCs), which fight infection; and platelets, which play a part in the clotting of the blood. The white blood cells can be further subdivided into three main types: the granulocytes, monocytes, and the lymphocytes.

The granulocytes, as their name suggests, have granules (particles) inside them. These granules contain special proteins (enzymes) and several other substances that can break down chemicals and destroy microorganisms such as bacteria. Monocytes are also important in defending the body against pathogens.

The lymphocytes form the third type of white blood cell. There are two main types of lymphocytes: T lymphocytes and B lymphocytes. They have different functions within the immune system. The B cells protect the body by making antibodies. Antibodies are proteins that can attach to the surfaces of bacteria and viruses. This attachment sends signals to many other cell types to come and destroy the antibody-coated organism. The T cell protects the body against viruses. When a virus enters a cell, it produces certain proteins that are projected onto the surface of the infected cell. The T cells can recognize these proteins and produce certain chemicals (cytokines) that are capable of destroying the virus-infected cells. In addition, the T cells can destroy some types of cancer cells.

Chronic leukemias develop very gradually. The abnormal lymphocytes multiply slowly, but in a poorly regulated manner. They live much longer than normal cells and thus their numbers build up in the body. The two types of chronic leukemias can be easily distinguished under the microscope. Chronic lymphocytic leukemia (CLL) involves the T or B lymphocytes. In chronic myelocytic leukemia (CML), the cells affected are the granulocytes. In addition, CML involves abnormalities of both the blood platelets, structures that help blood to clot, and the red blood cells, the blood cells that carry oxygen.

Very rarely will CML appear in children. Juvenile CML is a distinct disease of children younger than 14 years of age. There is a decrease in the number of blood platelets, substances that help the blood to clot. And there is an increase in certain white blood cells.!

Demographics

Slightly more men than women are affected by CML. The average patient is between 50 and 60 years of age. However, CML can affect people of any age. Chronic leukemias account for 1.2% of all cancers. Chronic myelocytic leukemia is generally seen in people in their mid-40s. According to the estimates of the

American Cancer Society (ACS), approximately 4,400 new cases of leukemia were diagnosed in the year 2000, 2,600 in men and 1,800 in women. Between 1973 and 1991, the rate at which CML appeared in the United States decreased slightly.

Causes and symptoms

People exposed to nuclear and other radiation are at increased risk for CML. Thus, people who have had higher exposure to radiation for medical reasons are at increased risk of developing this cancer. Parents with CML do not have children who are more than normally likely to develop CML. However, it is possible that people whose immune system exhibits certain characteristics are at increased risk for the disease.

CML develops in a two- or three-stage progression. First, the chronic phase appears. Between 60 and 80 percent of patients next exhibit the symptoms of what is called the accelerated phase. The final stage of CML is the terminal blastic phase.

Symptoms of chronic phase CML appear in 60%–85% of patients. This means 15% to 40% of all the people diagnosed with CML have no symptoms at all and are diagnosed with the disease only because of the results of a routine blood test. Patients who do have symptoms most frequently find themselves to have **fatigue**, **weight loss**, or pain. Some patients have a mass of tissue or an enlarged liver that the doctor is able to feel. Some patients experience strokes, visual problems, a lowering of alertness or responsiveness, priapism, and ringing in the ear. Many patients in accelerated phase CML have no specific symptoms. However, **fever**, weight loss, and **night sweats** may appear.

Patients with terminal, blastic phase CML often experience symptoms. There may be fever, weight loss, night sweats, and **bone pain**. Many patients develop infections. Many have anemia (low counts of red blood cells) and many bleed easily.

Diagnosis

There are no screening tests available for chronic leukemias. The detection of these diseases may occur by chance during a routine physical examination.

People who have CML have an unusually high number of white blood cells. Somewhat less than half of these people also have high numbers of blood platelets. Most patients have mild **anemia**. The composition of the bone marrow in CML patients also differs from that of a healthy person. The marrow is described as being hypercellular. This means that the number of cells present in the bone marrow is unusually great.

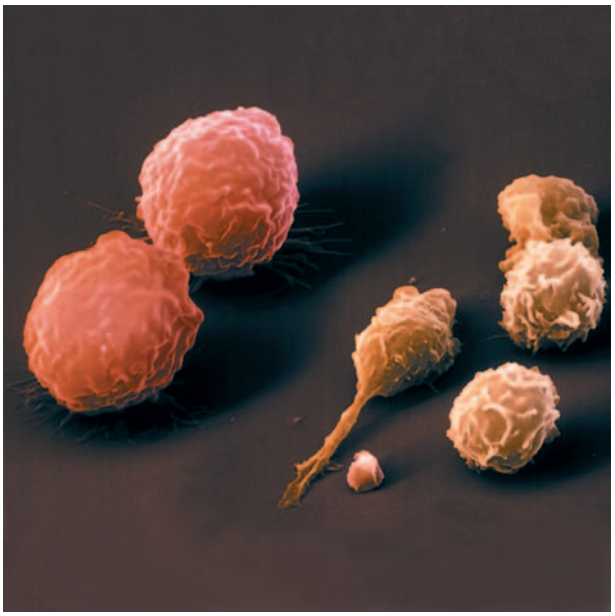
This spleen was removed from a patient with chronic myelocytic leukemia.The spleen has many functions—it removes old red blood cells, stores blood, and produces lymphocytes and plasma cells. Many blood disorders and cancers (including leukemias and lymphomas) can cause the spleen to enlarge. *(Custom Medical Stock Photo. Reproduced by permission.)*

If the doctor has reason to suspect leukemia, he or she will conduct a very thorough physical examination to look for enlarged lymph nodes in the neck, underarm, and pelvic region. Swollen gums, an enlarged liver or spleen, bruises, or pinpoint red rashes all over the body are among the signs of leukemia. Urine and blood tests may be ordered to check for microscopic amounts of blood in the urine and to obtain a complete differential blood count. This count will give the numbers and percentages of the different cells found in the blood.

Standard imaging tests such as x rays, **computed tomography** scans (CT scans), and **magnetic resonance imaging** (MRI) may be used to check whether the leukemic cells have invaded other organs of the body, such as the bones, chest, kidneys, abdomen, or brain.

Many doctors consider the presence of the Philadelphia (Ph) chromosome to be a crucial factor in the diagnosis of CML. The Ph chromosome is formed if some of the genetic material in two specific parts of two specific genetic units, called chromosomes, have exchanged some content in a particular way and created an arrangement of genetic material characteristic of CML patients.

Laboratory findings indicate when a patient enters the accelerated phase of CML. There may be more than 15% blasts (immature cells) in the blood. Alternately, the accelerated phase has started when more than 30% of the blood may be composed of a combination of blasts and promyelocytes. Promyelocytes are immature granulocytes. Another marker for the start of the accelerated phase is when the blood contains more than 20% of another white blood cell, called a basophil. Finally, the accelerated phase may be heralded by there being more than



Color-enhanced scanning electron microscope image of leukemia cells. Leukemia cells (left) are compared to healthy bone marrow cells. The leukemia cells are larger and have a higher metabolism than the normal cells. *(Copyright Meckes/Ottawa, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

100,000,000,000 platelets per liter of blood. The terminal, blastic phase of CML is heralded by measurements of 30% or more of blasts in either the bone marrow or the blood.

Clinical staging, treatments, and prognosis

Staging

Several different staging systems are in use. Most of these make use of the fact that a number of factors relevant to patients with CML say something about the patient's prognosis. Among these factors are the patient's age, the white blood cell count, the platelet count, the percentage of blast cells and basophil cells in either the blood or the bone marrow, the size of the liver, the size of the spleen, population of red blood cells that have a central portion called a nucleus, and the evolution of certain cell clones.

Treatment

It is very fortunate that several years ago the American Society of Hematology convened an Expert Panel on Chronic Myeloid Leukemia. This panel reviewed available therapies and published its findings in 1999. The findings were rigorously based upon evidence provided by the best research. The panel, comprised of top doctors from around the world, carefully sifted through all of the studies on treatment for CML and put aside all those studies performed with questionable methodology. This is a most important document relevant to CML therapy.

Since the publication of the findings of the expert panel, however, a new medicine has demonstrated great success in studies. This new medicine is known as STI571, **Imatinib mesylate**, or Gleevec. Since Gleevec was such a new drug in 2001, few studies have been conducted to evaluate its long-term effects. Furthermore, researchers have not had an opportunity to view the effects of imatinib mesylate over a period of five, 10, or 20 years.

In terms of CML therapy, the situation in 2001 was the following: physicians have the reliable report of the Expert Panel and a little bit of new information about a new medication. How the Expert Panel's findings and this new information should be integrated with the results of recent studies of imatinib mesylate is an issue that cancer doctors are currently resolving.

The Expert Panel looked at treatment of the chronic phase of CML. One therapy examined by the panel is **busulfan** (BUS). Another is **hydroxyurea** (HU). Both BUS and HU are **chemotherapy** medications. Studies have demonstrated that CML patients in chronic phase given HU live longer than patients given BUS.

Another therapy examined by the expert panel is interferon-alpha. Interferon is a chemical normally made in the cells of the body. It helps protect the body against viruses and also seems to have some effect against certain cancers. The interferon used as medicine is a laboratory-manufactured copy of the interferon produced by the body. The Expert Panel concluded that patients in chronic phase CML who have received interferon live longer than those given HU or BUS. This conclusion applies, in particular, to patients who have had little prior treatment for CML, who start interferon treatment soon after diagnosis, and who have certain other characteristics. However, side effects of interferon therapy are greater than those of therapy with HU or BUS. Patients who develop the side effects of interferon may feel like they have the flu. Patients receiving interferon seem to do better if they also receive chemotherapy with either HU or a medicine called Ara-C, or **cytarabine**.

Bone marrow transplantation (BMT) is an effective treatment for CML. In BMT, the patient's diseased bone marrow is replaced with healthy marrow. There are two ways of doing a bone marrow transplant. In an allogeneic bone marrow transplant, healthy marrow is taken from another person (donor) whose tissue is either the same or very closely resembles the patient's tissues. The donor may be a twin, a sibling, or a person who is not related at all. First, the patient's bone marrow is destroyed with very high doses of chemotherapy and

radiation therapy. To replace the destroyed marrow, healthy marrow from the donor is given to the patient.

In the second type of bone marrow transplant, called an autologous bone marrow transplant, some of the patient's own marrow is taken out and treated with a combination of anticancer drugs to kill all the abnormal cells. This marrow is then frozen to save it. The marrow remaining in the patient's body is then destroyed with high dose chemotherapy and radiation therapy. Following that, the patient's own marrow that was frozen is thawed and given back to the patient.

Allogeneic BMT may be used soon after diagnosis or after a patient has been treated with interferon or chemotherapy. The Expert Panel found that carefully designed, well-controlled, randomized studies have not been conducted on BMT therapy for CML. In the studies that do exist, scientists performed BMT on a group of patients and then observed the results. These studies show that BMT may lead to long-term remission. Remission is achieved if the disease becomes diminished for a period. Patients appear to live longer if they received chemotherapy followed by BMT. But the Expert Panel cautions that the results of these observational studies cannot be relied upon. One problem with them might be, for example, that the patients chosen to receive BMT might have started out being healthier than patients who did not receive BMT. The side effects of BMT may be severe, and a large number of CML patients receiving BMT die as a direct result of the BMT.

Therefore, one important consideration when BMT is being considered is whether the conditions under which the individual patient might receive BMT are favorable. In other words, is a very suitable marrow donor available? Is the patient within two years of CML diagnosis? It is important that patients understand clearly the ptential benefits and risks of BMT. One comment made by the Expert Panel is that younger patients who hope to live a very long time after CML diagnosis are more likely to benefit from allogeneic BMT. Autologous BMT has not achieved superior long-term results.

The recent studies of imatinib mesylate found it very effective in two groups of CML patients. One group was made up of patients who had unsuccessful results with interferon alfa therapy. The other group of CML patients studied were in the blast phase of the disease. Both studies found the medication to be effective and well tolerated. However, studies reporting on the effectiveness of imatinib mesylate over periods of five years or longer were not yet available in 2001.

Because leukemia cells can spread to all the organs via the blood stream and the lymph vessels, surgery is not considered an option for treating the leukemias.

KEY TERMS

Accelerated phase—The middle one of the three-phase course of CML. However, between 20 and 40 percent of patients never enter the accelerated phase but, rather, go directly from the chronic to the terminal blastic phase.

Basophil—A type of white blood cell

Blast—An immature cell

Bone marrow—Spongy tissue found in the large bones of the body

Chemotherapy—Treatment with drugs that act against cancer.

Chronic phase—The initial phase of CML.

Hypercellular—Bone marrow is described as being hypercellular if the number of cells present in the bone marrow is unusually great.

Leukapheresis — A procedure to remove or extract excessive white blood cells from the blood.

Philadelphia (Ph) chromosome — The Philadelphia (Ph) chromosome is present if some of the genetic material in two specific parts of two specific genetic units, called chromosomes, have exchanged some content in a particular way.

Remission—Remission of a disease is achieved if the disease becomes diminished for a period.

Terminal blastic phase—The final stage of CML.

The Expert Panel was careful to state that patient preferences should be taken into account as a treatment plan is developed. No approach to CML therapy is perfect. Each provides some benefit and is accompanied by certain side effects and risks. Which therapy or therapies is best for each individual patient depends upon on certain facts, such as the age of the patient and whether the patient is suffering from illnesses other than CML. In addition, the Expert Panel explains that the personal preferences of each patient are an important consideration. For example, some patients would rather avoid potential severe side effects and would be willing to give up the potential of living another few months or years. Other patients would be entirely unwilling to accept this way of looking at risks and benefits. It is important that health care professionals educate patients as to what treatment options are available and the perfections and imperfections associated with each. The opinions of each patient should be an important factor in deciding which treatment is best for that patient.

In the accelerated and blastic phase of CML, aggressive chemotherapy may be given. Combination chemo-

QUESTIONS TO ASK THE DOCTOR

- How can I obtain supportive care so I come through this not only alive but with my family and emotional life intact?
- What sort of benefit and what sort of side effects might each of the available treatment options bring?
- Would you please inform me about the treatment options and let me tell you about the priorities in my life so I can participate in forming a treatment plan?
- What is my prognosis?
- Are blasts present?
- Has complete remission or partial remission been achieved?
- What can I do to lower my risk of infection during chemotherapy?

therapy, in which multiple drugs are used, is more effective than using a single drug for the treatment. Interferon and BMT may be used, although results are not as good as for patients in the chronic phase of CML.

It should be mentioned that during treatment the doctor may order a procedure called leukapheresis. This lowers the numbers of white blood cells circulating in the patient's body. Also, either before or after therapy, it may be necessary to provide the patient with a transfusion of blood platelets. In addition, **antibiotics** are often used to help prevent infection in leukemia patients.

Prognosis

The most important factor in determining the likelihood that a patient receiving interferon therapy will achieve long-term survival is whether there is a positive response to interferon-alfa. Although experience with imatinib mesylate is being gathered in studies, this drug remains so new that doctors do not know what effect it will have on the prognosis of CML patients. Once the threat of transplantation-related complications has passed, patients receiving BMT may achieve longer survival than patients receiving interferon therapy.

Before the discovery of modern therapies, patients often spent between three-and-a-half and five years in the chronic phase. Then some patients entered an accelerated phase, from which most died within 18 months. Once patients were in the terminal, blastic phase most died within six months. However, all of this has changed with the arrival of newer therapeutic techniques. Just as many patients used to die from heart attack while similar patients may now live for decades, so cancer patients are achieving longer lives.

Coping with cancer treatment

Cancer patients need supportive care to help them come through the treatment period with physical and emotional strength in tact. Many patients experience feelings of **depression**, anxiety, and fatigue, and many experience **nausea and vomiting** during treatment. Studies have shown that these can be managed effectively if discussed with a doctor.

Prevention

Although some cancers are related to known risk factors, such as smoking, in leukemias, there are no definitive risk factors. Therefore, at the present time, there is no way known to prevent the leukemias from developing. People who are at an increased risk for developing leukemia because of proven exposure to ionizing radiation, the organic liquid benzene, or people who have a history of other cancers of the lymphoid system (Hodgkin's lymphoma) should undergo periodic medical checkups.

See also Chromosome rearrangements.

Resources

BOOKS

Braunwald, Eugene, et al. *Harrison's Principles of Internal Medicine*. 15th ed. New York: McGraw-Hill, 2001.

Humes, H. David, et al. *Kelley's Textbook of Internal Medicine*. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2000.

Pazdur, Richard, et al. *Cancer Management: A Multidisciplinary Approach: Medical, Surgical, & Radiation Oncology*. 4th ed. Melville, NY: PRR, 2000.

PERIODICALS

Drucker B. J., et al. "Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome." *New England Journal of Medicine* 344 (2001): 1038-1042.

Drucker, B. J., et al. "Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia." *New England Journal of Medicine* 344 (2001): 1031-1037.

Silver, Richard T., et al. "An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology." *Blood,* 94 (1999): 1517-1536.

ORGANIZATIONS

The American Cancer Society publishes useful texts, which include: *Adult Chronic Leukemia - Overview, Leukemia - Adult Chronic: Treatment, Leukemia - Adult Chronic: Detection and Symptoms, Leukemia: Adult Chronic FAQ [Frequently Asked Questions],* and *Leukemia - Adult Chronic: Prevention & Risk.* Telephone:1-800-ACS-2345. Web site: <www.cancer.org/>.

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Chronic myelogenous leukemia *see* **Chronic myelocytic leukemia**

Cigarettes

Description

Farmers were harvesting tobacco crops eight thousand years ago. Its uses since then have ranged from weather forecasting, appetite suppression, and pain relief, to the ceremonial smoking of the peace pipe and recreational use. Although tobacco was smoked and chewed in the United States back in the days of Columbus, it was not until the 1880s that smoking cigarettes became a widespread custom. At its peak in 1965, 52% of adult men and 32% of adult women in the United States routinely smoked. By the year 2002, smoking rates in the United States had decreased to 28.7% in men, and 23.4% in women; in 2004 they averaged 26% for all U.S. adults. Unfortunately, rates among young people may be rising again. A survey in Oregon in 2004 showed that by self-report, nearly 21% of girls and 18% of boys had tried smoking by seventh grade.

The potential adverse health effects of smoking were suspected as far back as 1859. It was then that an evaluation of 68 patients with oral cavity cancer linked 66 of them with the practice of smoking tobacco through short-stemmed clay pipes. Epidemiological evidence of the potentially harmful effects of cigarette smoking continued to mount over the following years. Finally, in 1962, the Royal College of Physicians of London officially deemed smoking a serious threat to health; in 1964 the U.S. Surgeon General followed suit.

Health risks of cigarette smoking

By 2001, an estimated 450,000 Americans died annually from diseases related to cigarette smoking. According to the American Cancer Society, 3,000 nonsmoking adults die each year of lung cancer from the effects of secondhand smoke. Pregnant women who smoke are more likely to give birth to low-weight babies, and smokers have increased rates of heart disease and respiratory problems.

In addition to those health risks, smokers are at a higher risk for the development of many types of cancer. In fact, 38% of all cancer deaths in men and 23% of all cancer deaths in women are believed to be attributed to cigarette smoking. As cigarette smoking becomes more prevalent in developing countries, the incidence of particular diseases, such as lung cancer, has also increased.

Cancers associated specifically with tobacco use include:

- Lung cancer. Smoking is now the primary modifiable risk factor for lung cancer. Tobacco was first linked to lung cancer in 1898, when it was thought to be the cause for several cases of lung cancers in tobacco workers. Since then, studies have continued to document the relationship between smoking and lung cancer. Lung cancer incidence—the number of new cases diagnosed per year—closely follows smoking trends. As more and more women began to smoke, for example, the incidence of lung cancer in women also increased. By the late 1900s, 90% of lung cancer cases in men and 79% in women were believed to be related to smoking. A 2004 study showed that smoking reduced-tar cigarettes did not lower lung cancer risk.
- Head and neck cancer. Smoking increases the risk of **head and neck cancers**. When tobacco is used in

conjunction with alcohol, there is believed to be an even higher risk of these diagnoses. The precise mechanism of this relationship, known as a "synergistic effect," is not yet well understood.

- Esophageal cancer: Smokers, particularly women smokers, are at an increased risk for developing esophageal cancer—a risk that increases with the quantity of cigarettes smoked per day.
- Pancreatic cancer: An estimated 22,000 people die from pancreatic cancer each year, and an alarming 30% of these deaths are related to cigarette smoking.
- Colorectal cancer. Individuals who smoke cigarettes are more likely to develop polyps in the colon, which in turn increases the risk of **colon cancer**. There is also evidence that the risk of colon and/or **rectal cancer** increases with pack years for smokers. (Pack years are calculated by multiplying the number of packs of cigarettes smoked a day by the number of years smoked.)
- **Stomach cancer**. Although some studies have found no existing relationship between smoking and stomach cancer, others have shown an increased risk for smokers over the age of 50 years and a relationship between the disease and pack-years of smoking. More conclusive research is necessary to better understand the role that smoking plays in the development of stomach, or gastric, cancer.
- **Bladder cancer**. Smoking is believed to be related to 30-40% of all bladder cancers, most of which are of the transitional cell type. The risk of developing bladder cancer is believed to be related to the duration of smoking and inversely related to the age at which smoking began (that is, the younger a person is when he or she starts smoking, the higher the chances of developing bladder cancer).
- **Cervical cancer**: There appears to be a relationship between smoking and cervical cancer—the higher the "dose," or amount smoked, the higher the likelihood of developing cervical cancer. Estimates show that smoking causes 1,200 cases of cervical cancer annually in Great Britain. Smoking is also associated with **human papilloma virus** infection, or HPV. Certain types of HPV can cause warts to develop in the genital area and cervix. These types of infections are a major cause of cervical cancer. Because of these overlapping relationships, the exact effect of smoking in cervical cancer needs further study.
- **Breast cancer**. Smoking was established as a risk factor for breast cancer by a large study of women in California that was published in 2004. Women who were current smokers had a 30% higher risk of breast cancer than women who had never smoked.

Although cancer is not always preventable, avoiding known risk factors, such as smoking, is an important part of prevention. The best approach to prevent disease is not to start smoking at all. However, even individuals who have smoked for years can decrease their risk of cancer and improve their health and well being by breaking the habit. Shortly after quitting smoking, a person will notice an improvement in their sense of taste and smell. Reducing the number of cigarettes smoked can help smokers successfully quit, says a new study from Yale University. However, just cutting back on the number of cigarettes, but continuing to smoke does little to reduce smoking's cancer risks.

After a smoke-free 10 years, lung cancer risk declines by up to 50%. After 15 smoke-free years, an ex-smoker has the same risk of early death than a person who never smoked at all. Although quitting smoking reduces the likelihood of cancer development, the risk depends upon the amount smoked, the number of years smoked, and whether or not a person is ill at the time of **smoking cessation**.

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Cimetidine *see* **Histamine 2 antagonists**

Ciprofloxacin *see* **Antibiotics**

Cisplatin

Definition

Cisplatin, also known by the brand name Platinol-AQ, Cis-platinum, CDDP, or DDP, is a **chemotherapy** medicine used to treat certain types of cancer by destroying cancerous cells.

Purpose

Cisplatin is approved by the Food and Drug Administration (FDA) to treat metastatic **testicular cancer** and metastatic **ovarian cancer**. It is also approved for late-stage **bladder cancer** and has been used to treat other types of cancer including head and neck cancer, **esophageal cancer**, **stomach cancer**, lung cancer, skin cancer, **prostate cancer**, **lymphoma** and others (breast, **neuroblastoma**, sarcoma, bladder, cervical, **myeloma**, **mesothelioma**, **osteosarcoma**).

Description

Cisplatin is a member of the group of chemotherapy drugs known as heavy metal alkylating-like agents. These drugs interfere with the genetic material (DNA) inside the cancer cells and prevent them from further dividing and growing more cancer cells.

Cisplatin has been used to treat cancer for more than 30 years. It can be used alone or in combination with other chemotherapies, including bleomycin-etoposide, **ifosfamide**, **gemcitabine**, **paclitaxel**, fluorouracil-leucovorin, **vinorelbine**, methotrexate-vinblastine-doxorubicin. Cisplatin may also be given with **radiation therapy**.

Recommended dosage

A cisplatin dose can be determined using a mathematical calculation that measures body surface area (BSA), which depends on a person's overall size. Body surface area is measured in the units known as square meter (m^2). The body surface area is calculated and then multiplied by the drug dosage in milligrams per m^2 (mg/m^2), which gives the proper dosage.

Cisplatin is a clear, colorless solution administered by an infusion into a vein. Infusions can be given once every three to four weeks over a 30 minutes up to two hours. It can also be given continuously over 24 hours a day for several days in a row. One cycle of cisplatin should not be given more frequently than once every three to four weeks. Dosages depend on the cancer being treated.

To treat metastatic testicular cancer

Dosages are 20 mg/m^2 per day administered into a vein every day for five days in a row. This regimen is used in combination with other chemotherapy drugs, mainly **bleomycin** and **etoposide** or **vinblastine**.

To treat metastatic ovarian cancer

Dosages are 50 mg/m^2 to 100 mg/m^2 administered into a vein once every four weeks. This regimen can be combined with the chemotherapy drug **cyclophosphamide** or **doxorubicin**.

To treat advanced bladder cancer

Cisplatin doses range from 50 mg/m^2 to 70 mg/m^2 administered into a vein once every 3 to 4 weeks. Cisplatin is usually given alone for bladder cancer.

Before receiving cisplatin large volumes of intravenous fluids are given to keep the kidneys flushed with water. If patients have severe kidney problems the physician will either not use cisplatin or decrease the dose being used.

Normal metal ions found in the body, called electrolytes, can be lost due to administration of cisplatin. These may be added to these intravenous fluids for replacement.

Precautions

When receiving cisplatin, it is important to drink a lot of fluids to help flush the kidneys and prevent kidney damage. Patients also receive additional fluids through their veins before, during, and after receiving cisplatin.

Blood counts will be monitored regularly while on cisplatin therapy. During a certain time period after receiving cisplatin, there is an increased risk of getting infections. Caution should be taken to avoid unnecessary exposure to crowds and people with infections.

Patients with a known previous allergic reaction to chemotherapy drugs or any other medications should tell their doctor.

KEY TERMS

Anemia—A red blood cell count that is lower than normal.

Chemotherapy—Specific drugs used to treat cancer.

DNA— Genetic material inside of cells that carries information to make proteins that are necessary to run the cells and keep the body functioning properly.

Electrolytes— Refers to the elements normally found in the body (sodium, potassium, calcium, magnesium, phosphorus, chloride, and acetate) that are important to maintain the many cellular functions and growth.

Food and Drug Administration (FDA)—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives approval to pharmaceutical companies for commercial marketing of their products.

Intravenous—To enter the body through a vein

Metastatic—Cancer that has spread to one or more parts of the body.

Neutropenia—a white blood cell count that is lower than normal.

Radiation therapy—The use of high-energy beams focused to treat cancerous tumors.

Patients who may be pregnant or trying to become pregnant should also tell their doctor before receiving cisplatin.

Chemotherapy can cause men and women to be sterile (not able to have children).

Patients should check with their doctors before receiving live virus **vaccines** while on chemotherapy.

An additional difficulty that can arise with cisplatin and other platinum-based anticancer drugs is that some tumor cells develop resistance to the drug. These resistant cells can then regrow and multiply. One strategy against drug resistance is to develop new drugs that can be used together with cisplatin to target resistant cells. In February 2004 the FDA approved pemetrexed (Alimta) for use together with cisplatin in the treatment of certain types of lung cancer. Another strategy for defeating tumor resistance to cisplatin is genetic modification of the resistant tumor cells. This approach in still in the early stages of experimentation as of 2004.

Side effects

Common side effects include **nausea and vomiting**, which can begin from 1 hour after receiving the drug and last as long as a week. Patients are given medicines known as **antiemetics**, before and after receiving cisplatin to help prevent or decrease this side effect. **Diarrhea** has also been known to occur.

A serious common side effect related to the total dose of cisplatin received is kidney damage, which can occur in up to one-third of patients. Taking fluids before, during and after receiving cisplatin help prevent this from occurring. In addition, some researchers in Brazil have reported that quercetin, a yellowish plant pigment found in apples and onions, shows promise as a protective treatment against kidney damage related to cisplatin.

Hearing damage can also occur in up to one-third of patients. Patients may experience ringing in the ears and hearing loss of high-pitched frequency. Hearing tests may be requested before and/or after cisplatin therapy. One promising treatment for cisplatin-related hearing damage is vitamin E, which is being studied by a group of researchers in Illinois.

Low blood counts, referred to as **myelosuppression**, are expected due to cisplatin administration. When the white blood cell count is low this is called **neutropenia** and patients are at an increased risk of developing a **fever** and infections. Platelets are blood cells in the body that allow for the formation of clots. When the platelet count is low, patients are at an increased risk for bruising and bleeding. Low red blood cell counts, referred to as **anemia**, may also occur due to cisplatin administration. Low red counts make people feel tired.

Cisplatin can also cause damage to nerves and nervous system tissues. Patients may feel tingling, numbness and sometimes burning of the fingers and toes. This side effect is common and can be severe.

Less common side effects include change of taste sensation, loss of appetite, dizziness, seizures, confusion, muscle cramps, and uncontrolled muscle contractions. Men treated with cisplatin for testicular cancer sometimes develop so-called dry ejaculations. Other side effects include, hair loss (alopecia), hiccups, rash, allergic reactions with difficulty breathing, swelling, and a fast heart rate.

Cisplatin may cause the body to waste normal electrolytes that circulate in the body (potassium, magnesium, phosphate, sodium, calcium) resulting in low levels of

these electrolytes. These will be monitored by the doctor and replacement drugs will be given if necessary.

All side effects should be reported to the doctor or nurse.

Interactions

Patients should avoid other drugs that may cause damage to the kidneys.

Certain water pills and cisplatin given together may increase the risk of hearing damage. Before starting any medications, patients should notify their doctors.

Cisplatin may make medications that control seizures less effective.

Resources

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ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657-3000. <www.ashp.org>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

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Cladribine

Definition

Cladribine, also known by the brand name Leustatin, is a **chemotherapy** medicine used to treat certain types of cancer by destroying cancerous cells.

Purpose

Cladribine is approved by the Food and Drug Administration (FDA) to treat active **hairy cell leukemia**. It has also been used to treat other types of leukemias and lymphomas.

Description

A member of the group of chemotherapy drugs known as a purine nucleoside analog, cladribine may also be referred to as 2-CdA, chlorodeoxyadenosine, and 2-chlorodeoxyadenosine. The purine nucleosides interfere with the genetic material (DNA) inside the cancer cells, cause DNA strand breaks, and block RNA synthesis. These traits help prevent cancer cells from further dividing and growing and also may cause the cancer cells to die.

Recommended dosage

Cladribine is a clear solution that is administered through a vein. The dose of cladribine is based on a patient's weight in kilograms. The approved dose for hairy cell leukemia is 0.09 mg per kilogram of body weight administered each day as a continuous intravenous infusion administered over 24 hours each day for seven continuous days. Some patients may receive this treatment in more than one cycle.

Other doses include 0.1 to 0.3 mg per kilogram of body weight per day for seven days administered as a continuous infusion. Patients may also receive cladribine as a two-hour infusion daily for five days in a row.

Precautions

Blood counts will be monitored regularly while on cladribine therapy. During a certain time period after receiving cladribine, there is an increased risk of getting infections. Caution should be taken to avoid unnecessary exposure to crowds and people with infection.

Patients with a known previous allergic reaction to chemotherapy drugs should tell their doctor.

Patients who may be pregnant or are trying to become pregnant should tell their doctors before receiving cladribine.

KEY TERMS

Anemia—A red blood cell count that is lower than normal.

Complete response—No sign of leukemia in the blood or bone marrow.

Chemotherapy—Specific drugs used to treat cancer.

DNA— Genetic material inside of cells that that carry information to make proteins that are necessary for proper cell functioning.

Food and Drug Administration—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives approval to pharmaceutical companies for commercial marketing of their products

Intravenous—To enter the body through a vein.

Neutropenia—White blood cell count that is lower than normal.

Although chemotherapy can cause men and women to be sterile (not able to have children), it is unknown if cladribine has this effect on humans.

Patients should check with their doctors before receiving live virus **vaccines** while on chemotherapy.

Side effects

The most common side effect from taking cladribine is low blood counts, referred to as **myelosuppression**. When the white blood cell count is lower than normal, referred to as **neutropenia**, patients are at an increased risk of developing a **fever** and infections. The platelet blood count can also be decreased due to cladribine administration, but generally returns back to normal within two weeks after the end of the infusion. Platelets are blood cells in the body that cause clots to form these clots stop bleeding. When the platelet count is low, patients are at an increased risk for bruising and bleeding. Cladribine causes low red blood cell counts, which is referred to as **anemia**. Low red counts make people feel tired and dizzy.

Other common side effects of cladribine include skin rashes or reactions, pain, redness, or swelling at the injection site. Half of patients with hairy cell leukemia experience a rash.

Patients may experience infections, chills, and fever when being treated with cladribine. This may result in treatment with **antibiotics**.

Nausea,vomiting, loss of appetite, abdominal pain, constipation and **diarrhea** are mild side effects from cladribine. If **nausea and vomiting** are a problem, patients can be given medicines known as **antiemetics** before receiving cladribine to help prevent or decrease these side effects.

Damage to the kidneys and nervous system tissues is uncommon with cladribine, unless given in high doses for bone marrow transplant patients. At high doses, kidney problems and nerve damage have resulted in weakness of the arms and legs.

Less common side effects of cladribine are hair loss, **itching**, a fever from taking the drug, lung problems, cough, inability to sleep, headache, dizziness, fast heart rate, muscle and joint aches, and **fatigue**.

Interactions

Patients should notify their doctors of any medications they are taking. In the case of cladribine, medications to make special note of include antithyroid agents, **azathioprine**, chloramphenicol, flucytosine, ganciclovir, interferon, **plicamycin**, zidovudine, probenecid, sulfinpyrazone.

Patients should tell their doctors if they have a known allergic reaction to **amifostine** or any other medications or substances, such as foods and preservatives. Before taking any new medications, including nonprescription medications, **vitamins**, and herbal medications, the patients should notify their doctors.

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Clinical trials

Definition

A clinical trial is a research study designed to answer specific medical questions regarding cancer care.

Description

The clinical trial is a scientific study that follows a written guideline (protocol) or recipe for treatment. It is the only scientific mechanism designed to test the effectiveness of new and promising therapies. The clinical trial provides intensive testing of new or updated treatment regimens. Almost all standard treatments in the field of oncology (cancer) originated from clinical trials.

These trials are conducted by medical, surgical and radiation oncologists (cancer specialists).

Cancer clinical trials are the key to preventing, diagnosing and treating all types of cancer. It is estimated that 60% of all cancer patients in the United States are being cured. Yet, fewer than 3% of adult cancer patients participate in clinical trials. In contrast, about 71% of children enter clinical trials. This has led to major advancements in treatment and high cure rates for many **childhood cancers** such as **Wilms' tumor** (malignant neoplasm of the kidney), **osteosarcoma** (tumor of the bone), and childhood leukemia (cancer of the blood).

Types of clinical trials

Clinical trials that involve new drugs or devices for humans must first be tested in animals. When a new or **investigational drug** has been discovered that shows anti-tumor activity in laboratory animals, it is tested on a small number of patients with different types of cancer, usually in a university setting. These are called Phase I trials and are designed to test the maximum tolerated dose (MTD) and side effects or toxicities of a new drug. This phase also helps determine how a new drug should be given (by mouth or by injection). The patients being tested are those with advanced cancer who have exhausted other treatment options. These patients may not personally benefit from participation in the trial.

If the investigational agent or drug continues to show anti-tumor activity and if the side effects are tolerable and not life-threatening, the drug is moved into a Phase II trial for further testing. In a Phase II trial, the drug is offered to a specific group of patients having the same tumor type. The drug is being tested to determine if it regresses tumor growth. Additional information on side effects of the treatment is also evaluated in this phase.

If the drug continues to show response to the patient's cancer, it is moved into a Phase III trial. At this phase, the investigational treatment is compared to the standard cancer therapy. This is to ensure that no one in a study is left without any treatment when standard treatment is available. If there is no standard therapy, a placebo (a pill that looks like the drug being studied but contains no active medication) may be used for comparison. However, researchers must inform potential patients of this possibility before patients decide whether to participate. Patients are usually assigned their treatment by a process called randomization, which is similar to the toss of a coin. Comparison or randomized trials help researchers find the most effective treatment for a specific type of cancer.

The objectives of Phase III trials include tumor response to treatment, survival, and quality of life during therapy. This phase can involve 400-1000 patients. Anti-tumor response by a significant proportion of the involved patients indicates that the investigational drug or treatment is ready to be submitted to the Food and Drug Administration (FDA) for approval. If approved, the drug is released from investigational status and made available for commercial use in patients with the specifically tested type of cancer.

KEY TERMS

Leukemia—Cancer of the blood and bone marrow.

Maximum tolerated dose (MTD)—The highest dose of an investigational drug that patients can tolerate without life-threatening or fatal side effects.

Oncology—The study of cancer.

Osteosarcoma—A tumor of the bone. The most common childhood cancer.

Placebo—A preparation without medication.

Protocol—A written, scientific guideline used for treatment planning in clinical trials.

Wilms' tumor—A malignant tumor of the kidney; occurs most frequently in children.

What to expect as part of a clinical trial

Taking part in a clinical trial does not mean that patients are seen as or treated like "guinea pigs," or that they will receive substandard care. Cancer patients who enroll in clinical trials may be the first to receive a new technique or drug that becomes the standard of care. Clinical trials, however, have risks, as well. The treatment or drug being tested is new, and the side effects may be unknown. The cancer patient, his or her loved ones, and the patient's physician must weigh the risks and benefits when deciding whether or not to enroll in a clinical trial.

When patients participate in a clinical trial, they receive treatment in a cancer center, hospital, clinic, and/or doctor's office. Doctors, nurses, social workers, and other health professionals may be part of the treatment team, and will closely monitor progress. Cancer clinical trial patients:

- are, as stated above, under close scrutiny
- are seen frequently by the members of the treatment team
- are tested often

QUESTIONS TO ASK THE DOCTOR

- Am I eligible for a clinical trial?
- Where can I get more information?

- follow the treatment plan their doctor prescribes and as according to the study's protocol
- and may also have other responsibilities, such as keeping a log or filling out health forms. Some studies continue to check on patients after their treatment is completed.

Resources

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Codeine *see* **Opioids**

Coenzyme Q10

Definition

Coenzyme Q10 is a fat-soluble nutrient also known as CoQ10, or ubiquinone. It is primarily found in the mitochondria, which are small bodies within cells that produce energy for the body. Apart from the important process that provides energy, CoQ10 also stabilizes cell membranes and acts as an antioxidant (a substance that reduces damage that results from oxygen, such as is caused by free radicals).

Purpose

Some people believe and anecdotal data suggest that oxygen-derived radicals are involved in the origins and development of cancer. Oxygen-derived radicals may cause damage to membranes, mitochondria, and large molecules, including proteins, lipids, and DNA. Accumulation of DNA damage may contribute to the development of cancer. There may be a relationship between oxidative stress and **breast cancer** development. People who subscribe to the belief that **antioxidants** are health-promoting may consume coenzyme Q10 (CoQ10) as one way of maintaining their health. However, as of 2005, this belief has not been conclusively proven by medical institutions.

Increased antioxidant enzyme activities may affect susceptibility of cells to cancer-causing agents and the response of tumor cells to **chemotherapy**. Administration of coenzyme Q10 by nutrition may induce the protective effect of coenzyme Q10 on breast tissue.

Furthermore, coenzyme Q10 is reputed to reduce the toxicity of some types of chemotherapy. **Doxorubicin**, a chemotherapeutic agent, is known to sometimes damage the heart. But use with coenzyme Q10 may reduce this toxic effect. People who are considering taking coenzyme Q10 should discuss its possible benefits of with a nutritionally oriented healthcare provider.

Description

Coenzyme Q10 appears to help ignite the cellular power stations that are necessary to maintain healthy cells, enhancing energy at the cellular level. The powerful antioxidant is highly concentrated in heart muscle cells. Coenzyme Q10 is believed by some to be an immune system booster and antioxidant that may help people avoid getting cancer, and it may be useful in treating it. Apart from its important function of providing energy, CoQ10 also stabilizes cell membranes, and as an antioxidant, it destroys free radicals in the body. These unstable molecules can cause damage to normal cells.

CoQ10 occurs naturally in many foods, which provide approximately half of the body's requirement. Cold-water fish such as mackerel, salmon, sardines, and tuna are particularly high in CoQ10. Meats and vegetable oils are also good sources. The human liver manufactures adequate amounts to fulfill the need not met in the diet. Some whole food nutritionists may believe that people who are deficient in B **vitamins**, selenium, vitamin C, or vitamin E may not be able to make as much coenzyme Q10 as they need since all these nutrients are required in order to produce it. The belief is that liver production and consumption of foods rich in CoQ10 may not provide the amounts needed to treat certain cancers, and for that reason, some people consume the enzyme in supplement form. It can be found formulated as capsules, gel caps, liquids, and tablets. The latter may be the best choice as it generally includes a source of fat that improves absorption. Vitamin E is a helpful stabilizing additive as well.

Coenzyme Q10 was first identified in 1957. Its chemical structure was determined in 1958. Interest in coenzyme Q10 as a potential treatment for cancer began in 1961, when a deficiency of the enzyme was noted in the blood of cancer patients. Low blood levels of coenzyme Q10 have been found in some patients with **myeloma** (a malignant tumor that develops in the blood-cell-producing cells of the bone marrow), **lymphoma** (cancer of the lymph nodes), and cancers of the breast, lung, prostate, pancreas, colon, kidney, and head and neck, according to the National Cancer Institute (NCI).

Recommended dosage

Coenzyme Q10 is usually taken by mouth as a tablet or capsule. It may also be given by injection into a vein. CoQ10 is available in oil-based capsules, powder-filled capsules, tablets, and liquid soft gels. The soft gels are believed to give higher absorption. Therapeutic dosages of CoQ10 for cancer range from 200 to 600 mg per day. As a general nutritional supplement, daily doses of CoQ10 range from 5 to 300 mg. Those who use CoQ10 for periodontal (the tissue around teeth) health may take 100–150 mg daily. The same dose range applies to those who take statin (cholesterol-lowering) drugs for treatment of high cholesterol. CoQ10 is best taken with food. About three weeks of daily dosing are necessary to reach maximum blood concentrations of CoQ10. It comes in the various dosages.

Precautions

Coenzyme Q10 should not be taken by persons who are allergic to it. Symptoms of an allergic reaction include breathing problems or tightness in the throat or chest, chest pain, and skin hives, rash, or itchy or swollen skin. No other known precautions are indicated for normal dosage.

Side effects

No serious adverse side effects have been reported. Some patients using coenzyme Q10 have experienced mild insomnia, elevated levels of liver enzymes, rashes, nausea, and upper abdominal pain. Other reported side effects have include dizziness, visual sensitivity to light, irritability, headache, heartburn, and **fatigue**.

KEY TERMS

Antioxidant—Any substance that inhibits the destructive effects of oxidation in the body.
Chemotherapy—The use of chemical agents to treat disease, especially cancer.
Lipids—Any of a group of organic compounds consisting of fats, oils, and related substances that, along with proteins and carbohydrates, are the structural components of living cells.
Lymphoma—Cancer of the lymph nodes.
Mitochondria—A small round or rod-shaped body that is found within most cells and produces enzymes for the metabolic conversion of food to energy.
Myeloma—A cancerous tumor that develops in the blood-cell-producing cells of the bone marrow.

Interactions

Patients should talk with their healthcare provider about possible interactions between CoQ10 and prescription drugs they may be taking. Certain drugs, such as those that are used to lower cholesterol or blood sugar levels, may reduce the effects of CoQ10. CoQ10 may also alter the body's response to **warfarin**, a drug that prevents the blood from clotting, and insulin, used to treat diabetes. The cholesterol-lowering drugs known as statins, such as lovastatin (Mevacor), simvastatin (Zocor), and pravastatin (Pravacol) may decrease CoQ10 levels in humans. It is likely that all statins have this effect. Also, CoQ10 may improve glycemic control in some type II diabetics. If this were to occur, antidiabetic medications might need appropriate adjusting. Some beta-blockers, in particular propanolol, may inhibit some CoQ10-dependent enzymes. Piperine, found in black pepper, may increase levels of CoQ10 in the blood.

Ken R. Wells

Cold sore *see* **Herpes simplex**

Colectomy

Definition

Colectomy is the surgical removal of all or part of the colon, the first part of the large intestine.

Purpose

Doctors perform colectomy to remove large Stage I **colon cancer** lesions or to cure colon cancer that: has spread beyond the mucous membrane, has infiltrated or spread beyond the intestinal wall, or is likely to recur.

Doctors also perform this procedure to improve patients' quality of life by relieving pain and preventing bleeding and other symptoms that occur when colon cancer invades organs near the bowel, and also, when non-surgical methods are unsuccessful, to treat diverticulitis, ulcerative colitis, and benign colon polyps.

Precautions

This surgery can significantly diminish bowel control and sexual function.

Description

Colectomy is the preferred therapy for colon cancers that can be cured. Performed in a hospital, under general anesthesia, this procedure involves removing the cancerous part of the colon, a margin of normal bowel, and any tissue or lymph nodes affected by the disease, and reconnecting the healthy segments of the colon (anastomosis). If infection or obstruction make it impossible to reconnect the colon, the surgeon creates an opening (stoma) in the abdominal wall (**colostomy**) through which feces passes from the body into a disposable collection bag.

Colostomy may be:

- temporary, with the ends of the intestines being reconnected at a later time, or
- permanent in patients whose cancer cannot be completely removed.

Open and laparoscopic procedures

Traditional, or open, colectomy is an invasive procedure requiring a wide surgical incision. This surgery allows the surgeon to view the internal organs very clearly.

Laparoscopic colectomy requires only a few small incisions, enables doctors to view the internal organs, and results in a shorter hospital stay and fewer side effects. Studies suggest that laparoscopic colectomy may be safer than open surgery for elderly patients. A clinical trial funded by the National Institutes of Health (NIH) is comparing survival rates for the two procedures.

Types of colectomy

LEFT RADICAL HEMICOLECTOMY Doctors perform left radical hemicolectomy to remove cancer and other abnormal tissue in the:

- descending colon, which extends from the pelvis to the spleen,

- and splenic flexure, the place where the descending colon joins the part of the large intestine that extends across the middle of the abdomen (transverse colon).

When cancer is found in the splenic flexure, the surgeon removes the splenic flexure, the first half of the descending colon, and about one-third of the transverse colon.

RIGHT RADICAL HEMICOLECTOMY Doctors perform this procedure to remove tumors and other abnormalities of the:

- section of large intestine nearest the appendix (cecum)
- portion of the large intestine that extends along the right side of the body from the small intestine to the transverse colon (ascending colon).

This procedure involves removing the cecum, descending colon, the hepatic flexure where the ascending colon joins the transverse colon, and the first one-third of the transverse colon. These procedures are considered radical because they involve removing nerves, blood vessels, and lymph nodes near the tumor.

TRANSVERSE COLECTOMY Performed to remove disease in the transverse colon, this procedure includes removing the:

- transverse colon,
- and hepatic and splenic flexures.

SIGMOID RESECTION Used to remove cancer in the part of the colon (sigmoid) between the descending colon and rectum, this procedure involves removing the:

- sigmoid colon
- bottom two-thirds of the descending colon

RECTOSIGMOID RESECTION Used to remove tumors in the part of the colon (rectosigmoid) just above the rectum (sigmoid flexure), this procedure removes:

- the sigmoid colon
- most of the rectum and surrounding rectal tissue (mesorectum) Because tumors in this part of the colon usually involve the bladder, uterus, or other organs, the surgeon may insert drainage tubes or a catheter to draw urine from the bladder.

ABDOMINOPERINEAL RESECTION (APR) This extensive procedure, which may be performed in two parts or by two surgical teams operating at the same time, involves removing the:

- lower sigmoid colon
- rectum

KEY TERMS

Diverticulitis—Inflammation or infection in pockets/ pouches that primarily develops in the wall of the large or small intestine.

Hemicolectomy—Surgical removal of half of the large intestine.

Hepatic—Of the liver.

Ulcerative colitis—Chronic inflammation of the large intestine and rectum.

- anus
- nearby lymph nodes, blood vessels, and nerves

Sphincter-saving APR is designed to minimize loss of bowel control by:

- removing only the tumor
- preserving nerves and blood vessels near the tumor.- These specialized procedures involve repositioning the tumor while removing it, can cause shedding of tumor cells, and may not be available in all hospitals.

After completing any of these procedures, the surgeon uses:

- sutures
- clips
- heat and electrical current (electrothermal bipolar vessel sealer)to tie off the ends of blood vessels before closing the incision.

Preparation

The day before the operation, the patient may consume only clear liquids, and may take nothing by mouth after midnight.

To reduce the possibility of infection, **antibiotics** are given to the patient the night before the operation.

Aftercare

A patient who has had an open colectomy will spend at least a week in the hospital and experience significant postoperative pain.

A patient who has had a laparoscopic colectomy will spend 4–5 days in the hospital, experience less pain, and resume normal activities within two weeks.

A patient who has had a colostomy must learn to care for the collection bag and keep the area clean. Patients who have had colostomies often worry about:

QUESTIONS TO ASK THE DOCTOR

- Which type of colectomy should I have?
- How will I feel and look after the operation?
- If I have to have a colostomy, will people be able to tell I'm wearing a bag?

- not being able to care for themselves
- odors, gas, and leakage from the collection bag
- health problems
- recurrence of cancerA patient who is depressed about sexual dysfunction, bowel problems, or other aspects of treatment may benefit from professional counseling or from joining a support group.

Risks

Side effects of colectomy include bladder complications, **diarrhea**, bowel irregularities, urinary urgency, and sexual dysfunction.

Normal results

Most patients experience postoperative pain. Patients who have laparoscopic surgery have less pain than patients who have open colectomy. Some patients require temporary colostomy until normal bowel function returns.

Most of these procedures do not affect sexual function, but rectosigmoid resection can make it difficult for a man to achieve erection during intercourse.

Abnormal results

Extensive surgery can cause:

- infection
- severe pain
- fecal incontinence
- prolonged recovery

Resources

OTHER

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Maureen Haggerty

Colon cancer

Definition

Cancer of the colon is the disease characterized by the development of malignant cells in the lining or epithelium of the first and longest portion of the large intestine. Malignant cells have lost normal control mechanisms governing growth. These cells may invade surrounding local tissue or they may spread throughout the body and invade other organ systems.

Synonyms for the colon include the large bowel or the large intestine. The rectum is the continuation of the large intestine into the pelvis that terminates in the anus.

Description

The colon is a tubular organ beginning in the right lower abdomen. It ascends on the right side of the abdomen, traverses from right to left in the upper abdomen, descends vertically down the left side, takes an S-shaped curve in the lower left abdomen, and then flows into the rectum as it leaves the abdomen for the pelvis. These portions of the colon are named separately though they are part of the same organ.

- cecum, the beginning of the colon
- ascending colon, the right vertical ascent of the colon
- transverse colon, the portion traversing from right to left
- descending colon, the left vertical descent of the colon
- sigmoid colon, the s-shaped segment of colon above the pelvis

These portions of the colon are recognized anatomically based on the arterial blood supply and venous and lymphatic drainage of these segments of the colon. Lymph, a protein-rich fluid that bathes the cells of the body, is transported in small channels known as lymphatics that run alongside the veins of the colon. Lymph nodes are small filters through which the lymph

travels on its way back to the bloodstream. Cancer can spread elsewhere in the body by invading the lymph and vascular systems. Therefore, these anatomic considerations become very important in the treatment of colon cancer.

The small intestine is the continuation of the upper gastrointestinal tract responsible for carrying ingested nutrients into the body. The waste left after the small intestine has completed absorption of nutrients amounts to a few liters, (about the same as quart), of material per day and is directly delivered to the colon, (at the cecum), for processing. The colon is responsible for the preservation of fluid and electrolytes as it propels the increasingly solid waste toward the rectum and anus for excretion.

When cells lining the colon become malignant, they first grow locally and may invade partially or totally through the wall of the bowel and even into adjacent structures and organs. In the process, the tumor can penetrate and invade the lymphatics or the capillaries locally and gain access to the circulation. As the malignant cells work their way to other areas of the body, they again become locally invasive in the new area to which they have spread. These tumor deposits, originating from the colon primary tumor, are then known as metastases. If metastases are found in the regional lymph nodes from the primary, they are known as regional metastases, or regional nodal metastases. If they are distant from the primary tumor, they are known as distant metastases. The patient with distant metastases has systemic disease. Thus the cancer originating in the colon begins locally and, given time, can become systemic.

By the time the primary tumor is originally detected it is usually larger than one cm (about 3/8 in) in size and has over one million cells. This amount of growth itself is estimated to take about three–seven years. Each time the cells double in number, the size of the tumor quadruples. Thus like most cancers, the part that is identified clinically is later in the progression than would be desired and screening becomes a very important endeavor to aid in earlier detection of this disease.

Demographics

There are at least 100,000 cases of colon cancer diagnosed per year in the United States. Together, colon and rectal cancers account for 10% of cancers in men and 11% of cancers in women. It is the second most common site-specific cancer affecting both men and women. A 2003 study reported that for unknown reasons, women are more likely to have advanced colon cancer at diagnosis than men. Nearly 57,000 people died from colon and rectal cancer in the United States in 2003. In recent years the incidence of this disease has decreased slightly, as has the mortality rate. It is difficult to tell if the decrease in mortality reflects earlier diagnosis, less death related to the actual treatment of the disease, or a combination of both factors.

Cancer of the colon is thought to arise sporadically in about 80% of those who develop the disease. Twenty percent of people are thought to have genetic predisposition, meaning their genes carry a trigger for the disease. Development of colon cancer at an early age, or at multiple sites, or recurrent colon cancer, suggests a genetically transmitted form of the disease as opposed to the sporadic form.

Causes and symptoms

Causes

Causes of colon cancer often are environmental in sporadic cases (80%) and sometimes genetic (20%). Since malignant cells have a changed genetic makeup, this means that in 80% of cases, the environment spontaneously induces change, whereas those born with a genetic predisposition are either destined to get the cancer or less environmental exposure can induce the cancer. Exposure to agents in the environment that may induce mutation is the process of carcinogenesis and is caused by agents known as carcinogens (cancer-causing agents). Specific carcinogens have been difficult to identify; however, dietary factors seem to be involved.

Colon cancer is more common in industrialized nations. Diets high in fat, red meat, total calories, and alcohol seem to predispose people to the disease. Diets high in fiber appear to decrease risk. High-fiber diets may help lessen exposure of the colon lining to carcinogens from the environment, as the transit time through the bowel is faster with a high-fiber diet than it is with a low fiber diet.

Age plays a definite role in the predisposition to colon cancer. Two-thirds of all cases occur after age 50 and the average age for those who develop the disease is 62.

There is also a slight increase risk for colon cancer in the individual who smokes.

Patients who suffer from inflammatory diseases of the colon known as ulcerative colitis and Crohn's colitis are also at increased risk.

Researchers know there is a genetic link to many cases of colon cancer, those called familial cases. This is the type of colon cancer that tends to run in families. In late 2003, a team of researchers identified the specific location on a human chromosome by analyzing blood samples from 53 families in which at least one member had a colon cancer or precancerous colon polyp. At least

200 genes exist on the location of chromosome 9, however, so the research will continue to identify the particular gene responsible for the cancer.

The development of polyps of the colon almost always precedes the development of colon cancer by five or more years. Polyps are benign growths of the colon lining. They can be unrelated to cancer, precancerous, or malignant. Polyps, when identified, are removed for diagnosis. If the polyps are benign, the patient should undergo careful surveillance for the development of more polyps or the development of colon cancer.

Symptoms

Colon cancer causes symptoms related to its local presence in the large bowel or by its effect on other organs if it has spread. These symptoms may occur alone or in combination:

- a change in bowel habit
- blood in the stool
- bloating, persistent abdominal distention
- constipation
- a feeling of fullness even after having a bowel movement
- narrowing of the stool—so-called ribbon stools
- persistent, chronic **fatigue**
- abdominal discomfort
- unexplained **weight loss**
- and, very rarely, nausea and vomiting

Most of these symptoms are caused by the physical presence of the tumor mass in the colon. Similar symptoms can be caused by other processes; these are not absolutely specific to colon cancer. The key is recognizing that the persistence of these types of symptoms without ready explanation should prompt the individual to seek medical evaluation.

If a tumor develops in the colon, it will begin to cause symptoms as it reaches a certain size. The symptoms are caused by the tumor blocking the opening in the colon. In addition, the tumor commonly oozes blood that is lost in the stool. (Often, this blood is not visible.) This results in anemia and chronic fatigue. Weight loss is a late symptom, often implying substantial obstruction or the presence of systemic disease.

Diagnosis

Screening

In all other cancers (breast and prostate, for example), screening tests look for small, malignant lesions. Screening for colorectal cancers, however, is the search for pre-malignant, benign polyps. This screening can be close to 100% effective in preventing cancer development, not just in detecting small cancers.

Screening involves physical exam, simple laboratory tests, and the visualization of the lining of the colon. To visualize the colon epithelium, clinicians use with x rays (indirect visualization) and endoscopy (direct visualization).

The physical examination involves the performance of a digital rectal exam (DRE). The DRE includes manual examination of the rectum, anus and the prostate. During this examination, the physician examines the anus and the surrounding skin for hemorrhoids, abscesses, and other irregularities. After lubricating the gloved finger and anus, the examiner gently slides the finger into the anus and follows the contours of the rectum. The examiner notes the tone of the anus and feels the walls and the edges for texture, tenderness and masses as far as the examining finger can reach. At the time of this exam, the physician checks the stool on the examining glove with a chemical to see if any occult (invisible), blood is present. At home, after having a bowel movement, the patient is asked to swipe a sample of stool obtained with a small stick on a card. After three such specimens are on the card, the card is then easily chemically tested for occult blood also. (The stool analysis mentioned here is known as a **fecal occult blood test**, or FOBT, and, while it can be helpful, it is not 100% accurate—only about 50% of cancers are FOBT-positive.) These exams are accomplished as an easy part of a routine yearly physical exam.

Proteins are sometimes produced by cancers and these may be elevated in the patient's blood. When this occurs, the protein produced is known as a tumor marker. There is a tumor marker for some cancers of the colon; it is known as carcinoembryonic antigen, or CEA. Unfortunately, this protein may be made by other adenocarcinomas as well, or it may not be produced by a particular colon cancer. Therefore, screening by chemical analysis for CEA has not been helpful. CEA has been helpful when used in a follow-up role for patients treated for colon cancer if their tumor makes the protein.

Indirect visualization of the colon may be accomplished by placing barium through the rectum and filling the colon with this compound. Barium produces a white contrast image of the lining of the colon on **x ray** and thus the contour of the lining of the colon may be seen. Detail can be increased if the barium utilized is thinned and air also introduced. These studies are known as the **barium enema** (BE), and the double contrast barium enema (DCBE).

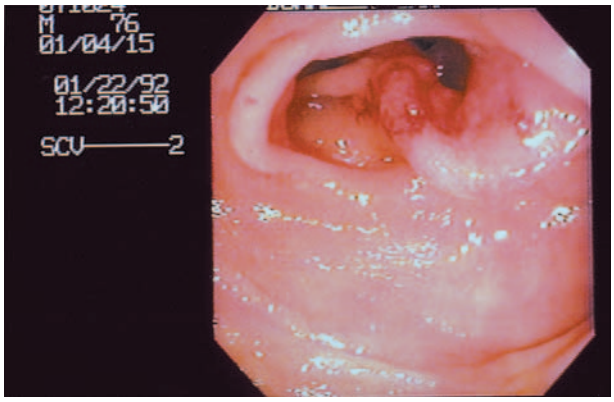
Direct visualization of the colon lining is accomplished using a scope or endoscope. The physician introduces the instrument through the rectum. Older, shorter scopes were rigid. Today, utilizing fiberoptic technology, the scopes are flexible and can reach much farther. If the left colon only is visualized, it is called flexible **sigmoidoscopy**. When the entire colon is visualized, the procedure is known as **colonoscopy**.

A procedure called virtual colonoscopy has been developed but debate continues on whether or not it is effective as colonoscopy. Virtual colonoscopy refers to the use of imaging, usually with computed tomography (CT) scans or magnetic resonance imaging (MRI) to produce images of the colon. Studies in late 2003 showed that virtual colonoscopy was as effective as colonoscopy for screening purposes and it offered the advantage of being less invasive and less risky. However, many physicians were unwilling to accept it as a replacement for colonoscopy, particularly since some patients might still require the regular colonoscopy as a follow-up to the virtual procedure if a polyp or abnormality is found that requires biopsy.

Unlike the indirect visualizations of the colon (the BE and the DCBE), the endoscopic screenings allow the physician to remove polyps and **biopsy** suspicious tissue. (A biopsy is a removal of tissue for examination by a pathologist.) For this reason, many physicians prefer endoscopic screening. All of the visualizations, the BE, DCBE, and each type of endoscopy, require preprocedure preparation (evacuation) of the colon.

The American Cancer Society has recommended the following screening protocol for those at normal risk over 50 years of age:

- yearly fecal occult blood test
- flexible sigmoidoscopy at age 50
- flexible sigmoidoscopy repeated every 5 years
- double contrast barium enema every five years
- colonoscopy every 10 years The American Gastroenterologial Association revised its screening guidelines in 2003 to recommend that people with two or more first-degree relatives with colorectal cancer or a first-degree relative with colon or rectal cancer before age 60 should have a screening colonoscopy beginning at age 40 or beginning 10 years prior to the age of the earlier colon cancer diagnosis in their family (whichever is earliest). Those with a first-degree relative diagnosed with colon cancer after age 60 or two second-degree relative with colon or rectal cancer should begin screening at age 40 with one of the methods listed above, such as annual sigmoidoscopy.



An endoscopic view of a colorectal tumor. *(Custom Medical Stock Photo. Reproduced by permission.)*

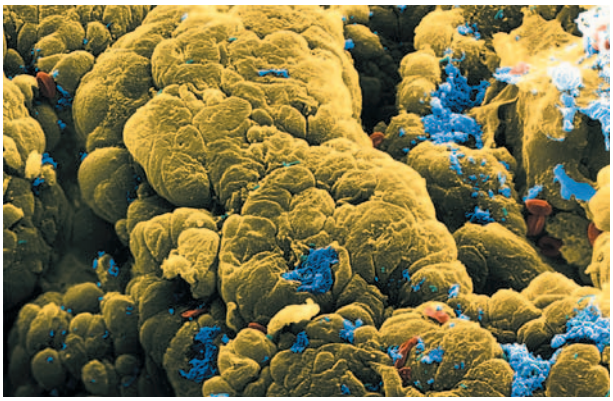
Evaluation of patients with symptoms

If patients have symptoms that could possibly be related to colon cancer, the entire colon will be examined. The combination of a flexible sigmoidoscopy and DCBE may be performed, but the preferred evaluation of the entire colon and rectum is a complete colonoscopy. Colonoscopy allows direct visualization, photography, and the opportunity to obtain a biopsy of any abnormality visualized. If, for technical reasons, the entire colon is not visualized endoscopically, a DCBE should complement the colonoscopy.

The diagnosis of colon cancer is actually made by the performance of a biopsy of any abnormal lesion in the colon. When a tumor growth is identified, it could be either a benign polyp (or lesion) or a cancer; the biopsy resolves the issue. The endoscopist may take many samples to exclude any sampling errors.

If the patient has advanced disease at the time of diagnosis, areas where the tumor has spread (such as the liver) may be amenable to biopsy. Such biopsies are usually obtained using a special needle under local anesthesia.

Once a diagnosis of colon cancer has been established by biopsy, in addition to the physical exam, studies will be performed to assess the extent of the disease. Blood studies include a complete blood count, liver function tests, and a CEA. **Imaging studies** will include a chest x ray and a CAT scan (**computed tomography** scan) of the abdomen. The chest x ray will determine if the cancer has spread to the lung, the CAT scan will evaluate potential spread to the liver as well as any local spread of the primary tumor. If the patient has any neurologic symptoms, a CAT scan of the brain will be performed, and if the patient is experiencing **bone pain**, a bone scan also will be performed.



Scanning electron micrograph (SEM) image of the inner surface of the human colon diseased with cancer. *(Copyright Oliver Meckes, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Treatment team

The surgeon and the medical oncologist each have a role in therapy that is dictated by the degree of progression of the disease. A radiation oncologist may also play a role on the team; however, radiation treatment is rare in colon cancer.

Clinical staging, treatments, and prognosis

Clinical staging

Once the diagnosis has been confirmed by biopsy, the clinical stage of the cancer is assigned. Using the characteristics of the primary tumor, its depth of penetration through the bowel, and the presence or absence of regional or distant metastases, stage is derived. Often, the depth of penetration through the bowel or the presence of regional lymph nodes can't be assigned before surgery.

Colon cancer is assigned stages I through IV, based on the following general criteria:

- Stage I: the tumor is confined to the epithelium or has not penetrated through the first layer of muscle in the bowel wall.
- Stage II: the tumor has penetrated through to the outer wall of the colon or has gone through it, possibly invading other local tissue.
- Stage III: Any depth or size of tumor associated with regional lymph node involvement.
- Stage IV: any of previous criteria associated with distant **metastasis**.

With many cancers other than colon cancer, staging plays an important pre-treatment role to best determine treatment options. Almost all colon cancers are treated with surgery first, regardless of stage. Colon cancers through Stage III, and even some Stage IV colon cancers, are treated with surgery first, before any other treatments are considered.

Treatments

SURGERY Surgical removal of the involved segment of colon (colectomy) along with its blood supply and regional lymph nodes is the primary therapy for colon cancer. Usually, the partial colectomies are separated into right, left, transverse, or sigmoid sections based on the blood supply. The removal of the blood supply at its origin along with the regional lymph nodes that accompany it ensures an adequate margin of normal colon on either side of the primary tumor. When the cancer lies in a position such that the blood supply and lymph drainage between two of the major vessels, both vessels are taken to assure complete radical resection or removal (extended radical right or left colectomy). If the primary tumor penetrates through the bowel wall, any tissue adjacent to the tumor extension is also taken if feasible.

Surgery is used as primary therapy for stages I through III colon cancer unless there are signs that local invasion will not permit complete removal of the tumor, as may occur in advanced stage III tumors. However, this circumstance is rare, occurring in less than 2% of all colon cancer cases.

After the resection is completed, the ends of the remaining colon are reconstructed; the hook-up is called an anastomosis. Once healing has occurred, there may be a slight increase in the frequency of bowel movements. This effect usually lasts only for several weeks. Most patients go on to develop completely normal bowel function.

Occasionally, the anastomosis is risky and cannot be performed. When the anastomosis cannot be performed, a **colostomy** is performed instead. A colostomy is performed by bringing the end of the colon through the abdominal wall and sewing it to the skin. The patient will have to wear an appliance (a bag) to manage the stool. The colostomy may be temporary and the patient may undergo a hook-up at a later, safer date, or the colostomy may be permanent. In most cases, emergent colostomies are not reversed and are permanent.

RADIATION **Radiation therapy** is used as an adjunct to surgery if there is concern about potential for local recurrence post-operatively and the area of concern will tolerate the radiation. For instance, if the tumor invaded muscle of the abdominal wall but was not completely removed, this area would be considered for radiation. Radiation has significant dose limits when residual

bowel is exposed to it because the small and large intestine do not tolerate radiation well.

Radiation also is used in the treatment of patients with metastatic disease. It is particularly useful in shrinking metastatic colon cancer to the brain.

CHEMOTHERAPY **Chemotherapy** is useful for patients who have had all identifiable tumor removed and are at risk for recurrence (adjuvant chemotherapy). Chemotherapy may also be used when the cancer is stage IV and is beyond the scope of regional therapy, but this use is rare.

Adjuvant therapy is considered in stage II disease with deep penetration or in stage III patients. Standard therapy is treatment with fluorouracil, (5FU) combined with **leucovorin** for a period of 6 to 12 months. 5FU is an antimetabolite and leukovorin improves the response rate. (A response is a temporary regression of the cancer from chemotherapy.) Another agent, **levamisole**, (which seems to stimulate the immune system), may be substituted for leucovorin. These protocols reduce rate of recurrence by about 15% and reduce mortality by about 10%. The regimens do have some toxicity but usually are tolerated fairly well.

Similar chemotherapy may be administered for stage IV disease or if a patient progresses and develops metastases. Results show response rates of about 20%. Unfortunately, these patients eventually succumb to the disease, and this chemotherapy may not prolong survival or improve quality of life in Stage IV patients. **Clinical trials** have now shown that the results can be improved with the addition of another agent to this regimen. **Irinotecan** does not seem to increase toxicity but it improved response rates to 39%, added 2-3 months to disease-free survival, and prolonged overall survival by a little over two months. If the cancer is detected early, surgical removal of the tumor can lead to complete cure in 75%–90% of patients.

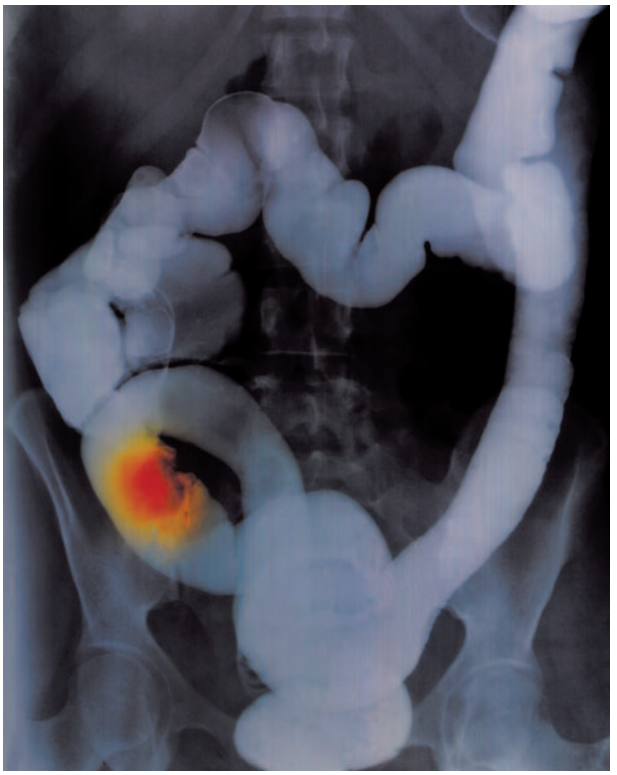
Prognosis

Prognosis is the long-term outlook or survival after therapy. Overall, about 50% of patients treated for colon cancer survive the disease. As expected, the survival rates are dependent upon the stage of the cancer at the time of diagnosis, making early detection crucial.

About 15% of patients present with stage I disease and 85-90% survive. Stage II represents 20-30% of cases and 65-75% survive. 30-40% comprise the stage III presentation of which 55% survive. The remaining 20-25% present with stage IV disease and are rarely cured.

Alternative and complementary therapies

Alternative therapies have not been studied in a large-scale, scientific way. Large doses of **vitamins**, fiber, and green tea are among therapies tried. Avoiding **cigarettes** and alcohol may be helpful. Before initiating any alternative therapies, the patient is wise to consult his or her physician to be sure that these therapies do not complicate or interfere with the established therapy.



Scanning electron micrograph (SEM) image of the inner surface of the human colon diseased with cancer. *(Copyright Oliver Meckes, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Coping with cancer treatment

For those with familial syndromes causing colon cancer, genetic counseling may be appropriate. Psychological counseling may be appropriate for anyone having trouble coping with a potentially fatal disease. Local cancer support groups may be helpful and are often identified by contacting local hospitals or the American Cancer Society.

The Colon Cancer Alliance offers internet online support at the following web page: <http://www.ccalliance.org/connect/support.html>.

Clinical trials

Clinical trials are scientific studies in which new therapies are compared to current standards in an effort to identify therapies that give better results.

KEY TERMS

Adenocarcinoma—Type of cancer beginning in glandular epithelium.

Adjuvant therapy—Treatment involving radiation, chemotherapy (drug treatment), or hormone therapy, or a combination of all three given after the primary treatment for the possibility of residual microscopic disease.

Anastomosis—surgical reconnection of the ends of the bowel after removal of a portion of the bowel.

Anemia—The condition caused by too few circulating red blood cells, often manifested in part by fatigue.

Carcinogens—Substances in the environment that cause cancer, presumably by inducing mutations, with prolonged exposure.

Electolytes—Salts, such as sodium and chloride.

Epithelium—Cells composing the lining of an organ.

Lymphatics—Channels that are conduits for lymph.

Lymph nodes—cellular filters through which lymphatics flow.

Malignant—Cells that have been altered such that they have lost normal control mechanisms and are capable of local invasion and spread to other areas of the body.

Metastasis—Site of invasive tumor growth that originated from a malignancy elsewhere in the body.

Mutation—A change in the genetic makeup of a cell that may occur spontaneously or be environmentally induced.

Occult blood—Presence of blood that cannot be seen with the naked eye.

Polyps—Localized growths of the epithelium that can be benign, precancerous, or harbor malignancy.

Radical resection—Surgical resection that takes the blood supply and lymph system supplying the organ along with the organ.

Resect—to remove surgically.

Sacrum—Posterior bony wall of the pelvis.

Systemic—Throughout the body.

Agents being tested for efficacy in patients with advanced disease include **oxaliplatin** and CPT-11. Please see reference below for current information available from the National Cancer Institute regarding these clinical trials.

Prevention

There is not an absolute method for preventing colon cancer. Still, there are steps an individual can take to dramatically lessen the risk or to identify the precursors of colon cancer so that it does not manifest itself. The patient with a familial history can enter screening and surveillance programs earlier than the general population. High-fiber diets and vitamins, avoiding obesity, and staying active lessen the risk. Avoiding cigarettes and alcohol may be helpful. By controlling these environmental factors, an individual can lessen risk and to this degree prevent the disease.

People who turn age 50, and all of those with a history of colon cancer in their families, should speak with their physicians about the most recent screening recommendations from physician and cancer organizations. They should watch for symptoms and attend all recommended screenings to increase the likelihood of catching colon cancer early.

Special concerns

Polyps are growths of the epithelium of the colon. They may be completely benign, premalignant or cancerous. The association of colon cancers in patients with certain types of polyps is such that it is thought that many polyps begin as a benign growth and later acquire malignant characteristics. There are two types of polyps, pedunculated and sessile. This terminology comes from their appearance; those that are pedunculated are on a stalk like a mushroom, and the sessile polyps are broad based and have no stalk. Unless a pedunculated polyp gets large, malignant potential is very small. This type may also be easily removed at colonoscopy, by a snaring technique. (A snare is like a lasso introduced through the endoscope to encircle the polyp at its base and amputate it.) The sessile polyp is also known as a villous **adenoma** and as many as 1/3 of these harbor a malignancy. Therefore, the villous adenoma is considered premalignant. Sessile polyps may or may not be able to be managed with the colonoscope and may need surgical removal because of their pre-malignant nature.

Polyps commonly present with occult blood in the stool. Since they are associated with the development of cancer, patients who have developed polyps need to enter a program of careful surveillance.

There is an occasional patient who develops a pattern of metastatic disease that is isolated to either the liver or the lung and the deposit appears to be solitary. When patients have this type of pattern of metastatic disease, especially if there has been a long interval between the primary management and the development of meta-

stasis, they may be considered for surgical resection of the isolated metastasis to effect a cure. In carefully selected patients, long-term survival approaching 20% has been achieved.

When a patient has developed metastatic cancer in the liver alone, a technique of administering chemotherapy directly to the liver is sometimes considered. This is called **hepatic arterial infusion** and requires the placement of a special device into the artery supplying the liver. This method of utilizing chemotherapy has been helpful in carefully selected patients only, and currently is not used as a cure.

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Teresa G. Odle

Colonoscopy

Definition

Colonoscopy is a medical procedure during which a long, flexible, tubular instrument called the colonoscope is used to view the entire inner lining of the colon (large intestine) and the rectum.

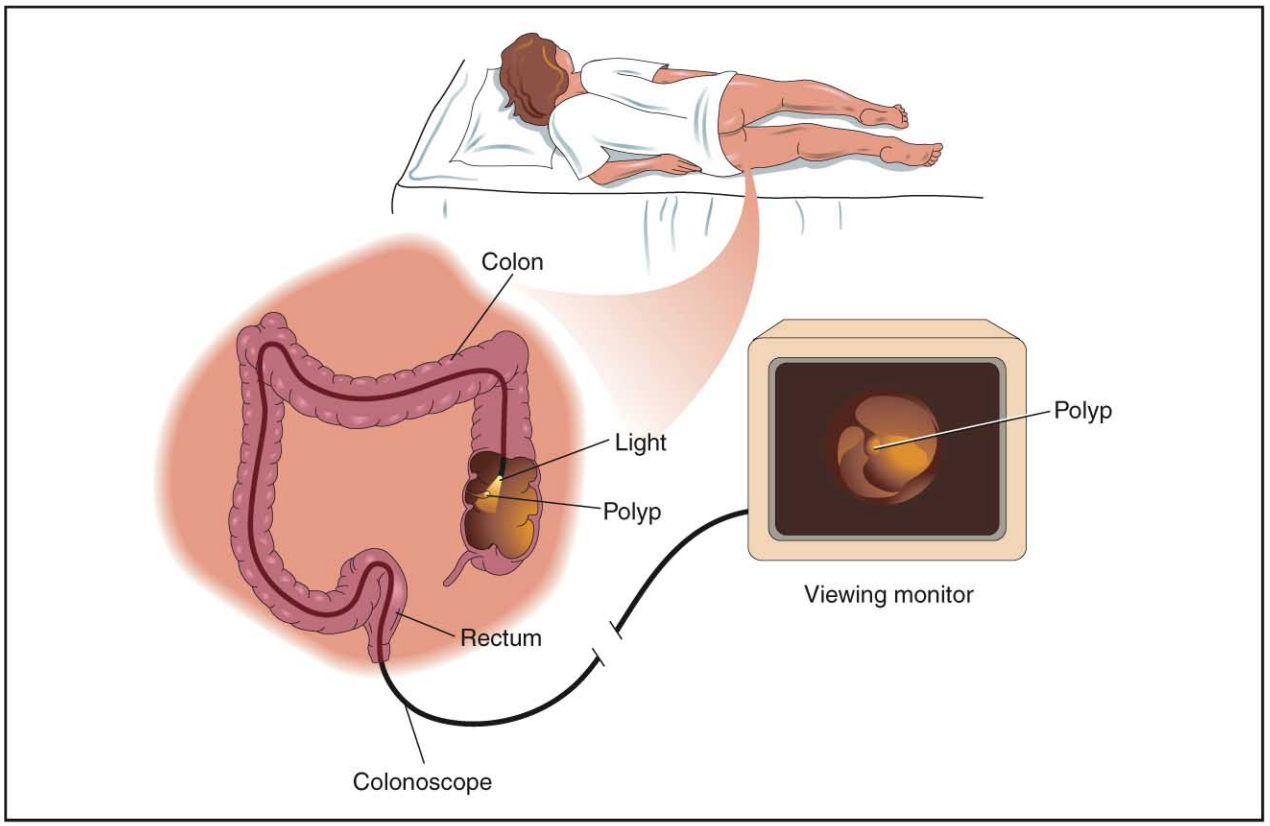
Purpose

A colonoscopy is generally recommended when the patient complains of rectal bleeding or has a change in bowel habits or other unexplained abdominal symptoms. The test is frequently used to test for colorectal cancer, especially when polyps or tumor-like growths have been detected using the **barium enema** and other diagnostic tests. Polyps can be removed through the colonoscope and samples of tissue (biopsies) can be taken to test for the presence of cancerous cells.

The test also enables the physician to check for bowel diseases such as ulcerative colitis and Crohn's disease. It is a necessary tool in monitoring patients who have a past history of polyps or **colon cancer**. It also may be used as a screening tool for people at high risk of developing colon cancer, such as those with a strong family history of the disease.

Precautions

Patients who are pregnant or have a history of heart and lung disease and those with blood-clotting problems should tell the doctor about their health history before the procedure. Special precautions may be needed. For instance, a patient with artificial heart valves or a history of infection of the lining of the heart may need to take **antibiotics** to prevent infection. Patients also should tell the doctor about all medications they are taking. The doctor may want the patient to stop taking some drugs, such as aspirin, for a period of time before the procedure. Patients with some intes-



Colonoscopy is a procedure in which a long, flexible, tubular instrument called a colonoscope is inserted into the patient's anus in order to view the lining of the colon and rectum. It is performed to test for colorectal cancer and other bowel diseases and it enables the physician to collect tissue samples for laboratory analysis. *(Illustration by Electronic Illustrators Group.)*

tinal conditions should not have a colonoscopy. Examples of these conditions include acute diverticulitis, acute inflamatory bowel disease, a suspected perforation or break in the intestines, and recent abdominal surgery. Patients must be able to cooperate during the procedure.

Description

The procedure can be done either in the doctor's office or in a special procedure room of a local hospital. An intravenous (IV) line will be started in a vein in the arm. Through the IV line, the patient generally receives a sedative and a pain-killer if needed.

During the colonoscopy, the patient will be asked to lie on his/her left side with his/her knees drawn up toward the abdomen. The doctor begins the procedure by inserting a lubricated, gloved finger into the anus to check for any abnormal masses or blockage. A thin, well-lubricated colonoscope then will be inserted into the anus and it will be gently advanced through the colon. The lining of the intestine will be examined through the scope. Air is pumped through the colonoscope to help clear the path or make it easier to view the lining of the colon. If there are excessive secretions, stool or blood that obstruct the viewing, they will be suctioned out through the scope. The doctor may press on the abdomen or ask the patient to change his/her position in order to advance the scope through the colon.

The entire length of the large intestine can be examined in this manner. If suspicious growths are observed, tiny biopsy forceps or brushes can be inserted through the colonoscope and tissue samples can be obtained. Small polyps also can be removed through the colonoscope. Biopsies and the removal of polyps through the colonoscope are both painless procedures. After the procedure, the colonoscope is slowly withdrawn and the instilled air is allowed to escape. The anal area is then cleansed with tissues.

The procedure may take anywhere from 30 minutes to one hour, depending on how easy it is to advance the scope through the colon.

The bowel cleaning preparation may be tiring and often produces **diarrhea** and cramping. During the colonoscopy, the sedative will keep the patient drowsy and relaxed. Most patients complain of minor discomfort, such as cramping or a feeling of fullness. However, the procedure is not painful.

A procedure called virtual colonoscopy has been developed but debate continues on whether or not it is effective as colonoscopy. Virtual colonoscopy refers to the use of imaging, usually with computed tomography (CT) scans or magnetic resonance imaging (MRI) to produce images of the colon. Studies in late 2003 showed that virtual colonoscopy was as effective as colonoscopy for screening purposes and it offered the advantage of being less invasive and less risky. However, many physicians were unwilling to accept it as a replacement for colonoscopy, particularly since some patients might still require the regular colonoscopy as a follow-up to the virtual procedure if a polyp or abnormality is found that requires biopsy.

Preparation

The doctor should be notified if the patient has allergies to any medications or anesthetics, has any bleeding problems, or if a female patient is pregnant. The doctor should also be informed of all the medications that the patient is currently taking and if he or she has had a barium x-ray examination recently. The doctor may instruct the patient not to take certain medications, like aspirin and anti-inflammatory drugs that interfere with clotting, for a period of time prior to the procedure. If the patient has had heart valves replaced or a history of an inflammation of the inside lining of the heart, the doctor should be informed, so that appropriate antibiotics can be administered to prevent any chance of infection. The risks of the procedure will be explained to the patient before performing the procedure and the patient will be asked to sign a consent form.

It is important that the colon be thoroughly cleaned before performing the examination. Before the examination, considerable preparation is necessary to clear the colon of all stool. The patient will be asked to refrain from eating any solid food for 24–48 hours before the test. Only clear liquids such as juices, broth, and gelatin are recommended. The patient is advised to drink plenty of water to avoid dehydration.

The day before the test, the patient will have to drink a special cleansing solution or take a strong laxative that the doctor has prescribed. The patient will also be given specific instructions as to how to use an enema, as a warm water enema may be necessary the next morning.

On the morning of the examination, one or two enemas of warm tap water may have to be taken. Generally, the procedure has to be repeated until the return from the enema is clear of stool particles. The patient is instructed not to eat or drink anything. The preparatory procedures are extremely important because the colon must be thoroughly clean for the exam to be performed.

Aftercare

After the procedure, the patient is kept under observation until the effects of the medications wear off. The patient will not be able to drive immediately after the procedure and can generally resume a normal diet and

KEY TERMS

Barium enema—An x-ray test of the bowel after giving the patient an enema of a white chalky substance that outlines the colon and the rectum.

Biopsy—Removal of a tissue sample for examination under the microscope to check for cancer cells.

Colonoscope—A thin, flexible, hollow, lighted tube that in inserted through the rectum into the colon to enable the doctor to view the entire lining of the colon.

Crohn's disease—A chronic inflammatory disease resulting from the immune system attacking one's own body. The disease generally affects the gastrointestinal tract and may cause the formation of deep ulcers.

Diverticulosis—A condition in which pouchlike sections that bulges through the large intestine's muscular walls but are not inflamed develop. They may cause bleeding, stomach distress, and excess gas.

Pathologist—A doctor who specializes in the diagnosis of disease by studying cells and tissues under a microscope.

Polyps—Abnormal growths that develop on the inside of a hollow organ such as the colon.

Ulcerative colitis—A chronic condition where recurrent ulcers are found in the colon. It is manifested clinically by abdominal cramping and rectal bleeding.

QUESTIONS TO ASK THE DOCTOR

- Did you see any abnormalities?
- How soon will you know the results of the biopsy (if one was done)?
- When can I resume any medications that were stopped?
- What future care will I need?

usual activities unless otherwise instructed. The patient will be advised to drink lots of fluids to replace those lost by **laxatives** and fasting.

For a few hours after the procedure, the patient may feel groggy. There may be some abdominal cramping and a considerable amount of gas may be passed. If a biopsy was performed or a polyp was removed, there may be small amounts of blood in the stool for a few days. If the patient experiences severe abdominal pain or has persistent and heavy bleeding, it should be brought to the doctor's attention immediately.

Risks

The procedure is considered safe. Very rarely (two in 1,000 cases) there may be a perforation (a hole) in the intestinal wall. Heavy bleeding due to the removal of the polyp or from the biopsy site occurs seldom occurs (one in 1,000 cases). Infections due to a colonoscopy are also extremely rare. Patients with artificial or abnormal heart valves are usually given antibiotics before and after the procedure to prevent an infection.

Normal results

The results are said to be normal if the lining of the colon is a pale reddish pink and no abnormal looking masses are found in the lining of the colon.

Abnormal results

Abnormal results would imply that polyps or other suspicious-looking masses were detected in the lining of the intestine. Polyps can be removed during the procedure and tissue samples can be biopsied. If cancerous cells are detected in the tissue samples, then a diagnosis of colon cancer is made. The pathologist analyzes the tumor cells further to estimate the aggressiveness of the tumor and the extent of spread of the disease.

Abnormal findings also could be due to inflammatory bowel diseases such as ulcerative colitis or Crohn's disease. A condition called diverticulosis, in which many small fingerlike pouches protrude from the colon wall, may also be identified.

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American Gastroenterological Association. 7910 Woodmont Ave., Seventh Floor, Bethesda, MD 20814. Phone: (301) 654-2055. <http://www.gastro.org>.

Cancer Research Institute (National Headquarters). 681 Fifth Avenue, New York, N.Y. 10022. (800) 992-2623. <http://www.cancerresearch.org>.

National Cancer Institute. 9000 Rockville Pike, Building 31, Room 10A31, Bethesda, Maryland, 20892. (800) 422-6237. <http://www.icic.nci.nih.gov>.

Society of American Gastrointestinal Endoscopic Surgeons (SAGES). 2716 Ocean Park Boulevard, Suite 3000, Santa Monica, CA 90405. (310) 314-2404. <http://www.sages.org>.

United Ostomy Association, Inc. (UOA). 19772 MacArthur Blvd., Suite 200, Irvine, CA 92612. (800) 826 0826. <http://www.uoa.org.>

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Colorectal cancer *see* **Colon cancer; Rectal cancer**

Colostomy

Definition

Ostomy is a surgical procedure used to create an opening for urine or feces to be released from the body. Colostomy refers to a surgical procedure in which a portion of the large intestine is brought through the abdominal wall to carry stool out of the body.

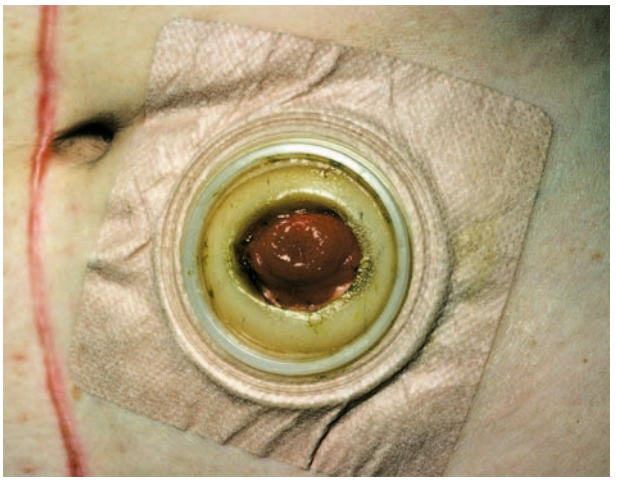
Purpose

A colostomy is created as a result of treatment for various disorders of the large intestine, including cancer, obstruction, inflammatory bowel disease, ruptured diverticulum, ischemia (compromised blood supply), or traumatic injury. Temporary colostomies are created to divert stool from injured or diseased portions of the large intestine, allowing rest and healing. These temporary colostomies are removed at a later date, with restoration of normal bowel function. Permanent colostomies are performed when the distal bowel (bowel at the farthest distance) must be removed or is blocked and inoperable. Although colorectal cancer is the most common indication for a permanent colostomy, only about 10–15% of patients with this diagnosis require a colostomy.

Description

Surgery will result in one of three types of colostomies:

- End colostomy. The functioning end of the intestine (the section of bowel that remains connected to the upper gastrointestinal tract) is brought out to the surface of the abdomen, forming the stoma by cuffing the intestine back on itself and suturing the end to the skin. A stoma is an artificial opening created to the surface of the body. The surface of the stoma is actually the lining of the intestine, usually appearing moist and pink, and it has no pain sensation. The distal portion of bowel (now connected only to the rectum) may be removed, or sutured closed and left in the abdomen. An end colostomy is usually a permanent ostomy, resulting from trauma, cancer or another pathological condition.
- Double–barrel colostomy. This colostomy involves the creation of two separate stomas on the abdominal wall. The proximal (nearest) stoma is the functional end that is connected to the upper gastrointestinal tract and will drain stool. The distal stoma, connected to the rectum and also called a mucous fistula, drains small amounts of mucus material. This is most often a temporary colostomy performed to rest an area of bowel, and to be later closed.



Colostomy stoma with ring for stoma bag. *(Custom Medical Stock Photo. Reproduced by permission.)*

- Loop colostomy. This colostomy is created by bringing a loop of bowel through an incision in the abdominal wall. An incision is made in the bowel to allow the passage of stool through the loop colostomy. In the past, a plastic rod was used to hold the loop in place, and this supporting rod was removed approximately 7-10 days after surgery, when healing had occurred. The use of the plastic supporting rod is becoming less common. A loop colostomy is most often performed for creation of a temporary stoma to divert stool away from an area of intestine that has been blocked or ruptured.

Preparation

As with any surgical procedure, the patient will be required to sign a consent form after the procedure is explained thoroughly. Blood and urine studies, along with various x rays and an electrocardiograph (ECG) may be ordered as the doctor deems necessary. If possible, the patient should visit an enterostomal therapist, who will mark an appropriate place on the abdomen for the stoma, and offer pre-operative education on ostomy management.

In order to empty and cleanse the bowel, the patient may be placed on a low-residue diet for several days prior to surgery. A liquid diet may be ordered for at least the day before surgery, with nothing by mouth after midnight. A series of enemas and/or oral preparations (GoLytely or Colyte) may be ordered to empty the bowel of stool. Oral **antibiotics** (neomycin, erythromycin, or kanamycin sulfate) may be given to decrease bacteria in the intestine and help prevent post-operative infection. A nasogastric tube may be inserted from the nose to the stomach on the day of surgery or during surgery to remove gastric secretions and prevent **nausea and vom-**

iting. A urinary catheter (a thin plastic tube) may also be inserted to keep the bladder empty during surgery, giving more space in the surgical field and decreasing chances of accidental injury.

Aftercare

Post-operative care for the patient with a new colostomy involves monitoring of blood pressure, pulse, respiration, and temperature. Breathing tends to be shallow because of the effect of anesthesia and the patient's reluctance to breathe deeply and experience pain caused by the abdominal incision. The patient is instructed how to support the operative site during deep breathing and coughing, and given pain medication as necessary. Fluid intake and output is measured, and the operative site is observed for color and amount of wound drainage.

Two to three days after the operation, the patient will be able to resume eating. For both open and laparoscopic resections, most patients are discharged from the hospital in five to seven days. Healing may take one to two months.

A colostomy pouch will generally have been placed on the patient's abdomen, around the stoma during surgery. During the hospital stay, the patient and caregivers will be educated about how to care for the colostomy. Determination of appropriate pouching supplies and a schedule of how often to change the pouch should be established. Regular assessment and meticulous care of the skin surrounding the stoma is important to maintain an adequate surface on which to apply the pouch. Some patients with colostomies are able to routinely irrigate the stoma, resulting in regulation of bowel function; rather than needing to wear a pouch, these patients may need only a dressing or cap over their stoma. Often, an enterostomal therapist will visit the patient at home after discharge to help the patient resume normal daily activities.

Risks

Potential complications of colostomy surgery include:

- excessive bleeding
- surgical wound infection
- thrombophlebitis (inflammation and blood clot to veins in the legs)
- pneumonia
- pulmonary embolism (blood clot or air bubble in the lungs' blood supply)

Normal results

Complete healing is expected without complications. The period of time required for recovery from the surgery varies depending on the patient's overall health prior to surgery. The colostomy patient without other medical complications should be able to resume all daily activities once recovered from the surgery.

KEY TERMS

Diverticulum—Pouches that project off the wall of the intestine, visible as opaque on an x ray after the patient has swallowed a contrast (dye) substance.

Embolism—Blockage of a blood vessel by any small piece of material traveling in the blood. The emboli may be caused by germs, air, blood clots, or fat.

Enema—Insertion of a tube into the rectum to infuse fluid into the bowel and encourage a bowel movement. Ordinary enemas contain tap water, mixtures of soap and water, glycerin and water, or other materials.

Intestine—Commonly called the bowels, divided into the small and large intestine. They extend from the stomach to the anus. The small intestine is about 20 ft (6 m) long. The large intestine is about 5 ft (1.5 m) long.

Ischemia—A compromise in blood supply delivered to body tissues that causes tissue damage or death.

Ostomy—A surgically created opening in the abdomen for elimination of waste products (urine or stool).

Abnormal results

The doctor should be made aware of any of the following problems after surgery:

- increased pain, swelling, redness, drainage or bleeding in the surgical area
- headache, muscle aches, dizziness or **fever**
- increased abdominal pain or swelling, constipation, nausea or vomiting or black, tarry stools

Stomal complications to be monitored include:

- Death (necrosis) of stomal tissue. Caused by inadequate blood supply, this complication is usually visible 12–24 hours after the operation and may require additional surgery.
- Retraction (stoma is flush with the abdomen surface or has moved below it). Caused by insufficient stomal length, this complication may be managed by use of

special pouching supplies. Elective revision of the stoma is also an option.

- Prolapse (stoma increases length above the surface of the abdomen). Most often results from an overly large opening in the abdominal wall or inadequate fixation of the bowel to the abdominal wall. Surgical correction is required when blood supply is compromised.
- Stenosis (narrowing at the opening of the stoma). Often associated with infection around the stoma or scarring. Mild stenosis can be removed under local anesthesia. Severe stenosis may require surgery for reshaping the stoma.
- Parastomal hernia (bowel causing bulge in the abdominal wall next to the stoma). Usually due to placement of the stoma where the abdominal wall is weak or creation of an overly large opening in the abdominal wall. The use of an ostomy support belt and special pouching supplies may be adequate. If severe, the defect in the abdominal wall should be repaired and the stoma moved to another location.

Resources

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ORGANIZATIONS

The United Ostomy Association, a self-help organization, provides useful information. 36 Executive Park, Suite 120, Irvine, CA 92714. Phone: (800) 826-0826 or (714) 660-8624. uoa@deltanet.com. <http://www.uoa.org.>.

Wound Ostomy and Continence Nurses Society. 2755 Bristol Street, Suite 110, Costa Mesa, CA 92626. (714) 476-0268. <http://www.wocn.org>.

Kathleen Dredge Wright

Complementary cancer therapies

Definition

Alternative and complementary therapies refer to treatments outside the mainstream of Western scientific medicine. They cover a wide variety of approaches, ranging from the medical systems of other cultures to special diets or medications, spiritual practices, herbal remedies, and external energy sources. As a general rule, *complementary* is used to refer to treatments that are offered alongside mainstream methods of cancer therapy to relieve the patient's discomfort or contribute to his or her overall sense of well-being. Other terms that are sometimes used for complementary therapies are *adjunctive*, which means helping or assisting, and *supportive*. Complementary or supportive treatments are not considered cures for cancer. When they are given together with mainstream cancer treatments, the combination is called *integrative* therapy.

The word *alternative* refers to treatments used instead of mainstream cancer treatments in an attempt to cure cancer. Some alternative treatments have not yet been tested by scientific researchers while others have been tested and shown not to work. If alternative remedies are used instead of proven cancer treatments, they may harm the patient by allowing the cancer to grow and reducing the chances of curing it by standard therapies. Treatments that are still being tested on animals or humans are called research or investigational therapies. In the United States, medications or other methods of treatment must be approved by the Food and Drug Administration (FDA) before they can be considered standard treatments for cancer. In 1991, Congress established the Office of Alternative Medicine as part of the National Institutes of Health. It includes the National Center for Complementary and Alternative Medicine, or NCCAM. As of October 2000, NCCAM supports 15 specialized research centers that study the safety and effectiveness of various complementary and alternative medicine (CAM) treatments for cancer.

Description

Today there are over two hundred complementary/alternative substances and treatment methods that have been given to cancer patients. They can be grouped for purposes of discussion into ten major categories.

Biologic

Biologic treatments are drugs or other medical products that are derived naturally from plants, animals, or the human body itself. They are thought to help the body fight cancer by restoring its biochemical balance.

Many biologic treatments have already been tested by researchers. They vary widely in their effectiveness:

- Antineoplaston therapy. Antineoplastons, which are extracted from blood serum and urine, are short-chain amino acids that supposedly reprogram the DNA of

cancer cells so that the cells reproduce normally instead of uncontrollably. The FDA and National Cancer Institute (NCI) have permitted **clinical trials** of antineoplastons in cancer patients. However, the clinical trials were closed in 1995 because of small enrollment numbers in the trials and lack of consensus about how to recruit more patients for the trials. Because of the small numbers in the trials, the NCI draws no conclusions about the effectiveness of antineoplastons. Antineoplaston therapy can be used with standard **chemotherapy**.

- 714X. 714X is a treatment consisting of three 21-day rounds of injections of camphor and organic salts directly into the lymphatic system. It is based on a theory that cancer cells use up large amounts of nitrogen and secrete a poisonous K-cofactor that paralyzes the immune system so that nitrogen can be drawn from healthy cells. Since the camphor in 714X contains nitrogen, the cancer cells do not have to secrete the K-cofactor, which in turn allows the immune system to recover.
- Cancell/Entelev. Cancell/Entelev is a liquid marketed as a treatment for cancer as well as AIDS, epilepsy, lupus, and other diseases. It is also sold as Cantron, Sheridan's Formula, Jim's Juice, and Crocinic Acid. Cancell is a mixture of 12 common chemicals—including nitric acid and sulfuric acid—none of which are known to be effective against cancer. The NCI tested Cancell four times between 1978 and 1991; no benefit to this therapy could be demonstrated, and the NCI decided not to study it further.
- Hydrazine sulfate. Hydrazine sulfate is a chemical that has been used to treat the loss of appetite (**anorexia**) and wasting away of body tissue (cachexia) that occur in late-stage cancer; it has not been promoted as a cure for cancer. It is available in the United States as a dietary supplement. Hydrazine sulfate has been studied by the Russian government as well as the NCI, but test results are not conclusive. As of 2001, no clinical trials of hydrazine sulfate are being conducted in the United States.
- Laetrile. Laetrile, which is also known as amygdalin or vitamin B_{17}, is a chemical found in fruit pits, lima beans, sorghum, and clover; it contains sugar and produces cyanide. The cyanide is considered to be the primary anti-cancer agent in laetrile. Laetrile has been used by itself to treat cancer and as part of metabolic therapy, but it has not shown any anti-cancer effectiveness in NCI clinical trials. It is not approved for use in the United States but is available in Mexico. When taken by mouth, laetrile can produce side effects resembling the symptoms of cyanide poisoning.
- Hydrogen peroxide therapy. Hydrogen peroxide has been used in the United States and Japan since the 1960s as an adjunctive treatment to **radiation therapy**. The hydrogen peroxide is diluted in water and injected directly into the patient's arteries. Some researchers think that hydrogen peroxide helps to shrink tumors by making them more sensitive to radiation.

Metabolic therapies

Metabolic therapies combine enzyme treatments, diets, and nutritional supplements with herbal medicines or special formulas. They are based on the belief that cancer results from many factors acting together, and that it should be treated by strengthening the entire body, not just by removing the tumor.

Most of these therapies are considered questionable by mainstream physicians:

- Kelley/Gonzalez therapy. Kelley/Gonzalez therapy focuses on cancer of the pancreas. Its practitioners regard cancer as resulting from inadequate levels of pancreatic enzymes, which help the body to digest protein. Kelley/Gonzalez therapy includes a diet tailored to each individual, nutritional supplements, digestive aids, enzyme supplements, and colonic irrigation. It is the most promising of the metabolic therapies. As of 2001, the NCI is conducting clinical trials of Kelley/Gonzalez therapy at Columbia University.
- Gerson therapy. Gerson therapy combines a low-salt vegan diet with large quantities of fruit and vegetable juices, as well as three or four coffee enemas each day to detoxify the body. It is based on the notion that cancer patients have too much sodium in their bodies and not enough potassium. Gerson therapy is not recommended as an alternative to conventional treatment for cancer.
- Issel's whole-body therapy. This form of metabolic therapy originated in Germany. It includes psychotherapy, oxygen therapy, and the removal of amalgam dental fillings (which contain small amounts of mercury) as well as a special diet.
- Revici therapy. Revici therapy is based on the belief that cancer is associated with imbalances in the body's tissue-building and tissue-breakdown processes. These imbalances are treated with intravenous injections of lipids (fatty or waxy organic substances) containing oxygen, copper, calcium, and selenium.

Immune enhancement therapies

Immune enhancement therapies are based on the theory that cancers in humans result from a weakened immune system.

Therapies in this category are not recommended as alternatives to conventional cancer treatment:

- Immuno-augmentative therapy (IAT). IAT is based on the theory that cancer results from an imbalance among four blood protein components, called the tumor antibody, the tumor complement, the blocking protein, and the deblocking protein. Treatment consists of injecting various amounts of these components to restore the proper balance.
- Livingston therapy. Livingston therapy uses a raw-food vegetarian diet combined with nutritional supplements and **vaccines** to restore the patient's immune system. It is based on a theory that cancer is caused by a bacterium called progenitor cryptocides, found in eggs, milk, poultry, and beef products.

Bodywork/movement therapies

Doctors often recommend bodywork and movement therapies as adjunctive treatments for cancer because they benefit patients emotionally as well as physically. The exercise involved in dance therapy, yoga, and t'ai chi helps to preserve muscle tone and joint flexibility. Therapeutic massage can relieve muscle soreness resulting from emotional stress.

Some common forms of body work and movement therapy include:

- Acupuncture and acupressure. Acupuncture is a basic form of treatment in traditional Chinese medicine. It involves the insertion of very thin steel needles into points on the body associated with the flow of vital energy. In acupressure, the energy points are stimulated by finger pressure. These forms of treatment are often combined with massage.
- Chiropractic. A chiropractor treats the patient's nervous system by manipulating or adjusting the segments of the spinal column. Some people find that chiropractic relieves back pain. As of 2001, one of the NCCAM's 15 research centers is specializing in studies of chiropractic.
- Yoga. Yoga is a good form of low-impact exercise for releasing stress and tension. Its stretches and poses can be modified to fit the needs or limitations of individual patients. Cancer patients who have had surgery should consult their doctor before starting a yoga program.
- T'ai chi. T'ai chi is a Chinese system of meditative exercise that involves a series of slow circular or stretching movements. Many patients find it relaxing and calming. In clinical settings, control groups practicing tai chi showed improvements in symptoms and signs such as strength, appetite, weight gain, stamina, and bowel function, hence increasing the ability for self-cure. In addition, t'ai chi and related practices are simple to learn and produce no side effects.
- Therapeutic massage. Therapeutic massage is often recommended as a complementary treatment to mainstream cancer therapy, but should not be given near the area of any recent surgery.
- Dance therapy. Dance therapy allows patients to release strong emotions as well as exercising their joints and muscles.

Diets and digestive treatments

These forms of treatment are based on the belief that the human digestive tract stores or produces toxic substances and should be cleansed periodically by special foods, fasting, or washing out the lower bowel.

Dietary therapies vary in their usefulness as complementary cancer treatments:

- Vegan diets. Vegan diets are vegetarian diets that omit eggs and dairy products as well as meat. They are thought to offer some protection against cancer, because the milk as well as the tissues of animals raised for meat may contain carcinogenic (cancer-causing) chemicals. In addition, the high fiber content of vegan diets appears to lower the risk of colon cancer.
- Fasting and juice therapies. These therapies are a major part of naturopathic treatment. Naturopaths maintain that the body can devote more of its energy to healing itself when it does not have to digest high-fat, high-calorie foods. In addition, they regard fasting as a way to help the body rid itself of toxic wastes.
- Macrobiotics. Macrobiotic diets originated in Japan, and classify foods according to the Eastern distinction between yin and yang rather than Western nutritional categories. These diets emphasize brown rice, fruits and vegetables eaten in season, and cooking over a flame rather than using electricity. Although macrobiotic diets have been credited with preventing or curing cancer, no scientific studies have verified these claims.
- Colonic irrigation. This is a treatment method that circulates warm water through the patient's large intestine to remove feces and toxic substances from the walls of the colon. It has been recommended by some alternative therapists for AIDS-related cancers.

Herbal therapies and food supplements

Herbal treatments are historically important because of their role in the development of a number of standard medications. Complementary herbal treatments are presently used to relieve the side effects of mainstream

cancer therapy, such as peppermint tea for nausea or ginger for **diarrhea**. Patients should, however, consult a health professional before taking any herbal preparation by mouth to make sure that the herb(s) will not interact with prescription medications. Fragrant herbs (rosemary, lemongrass, mint, etc.) can be added to massage oils or bath water for aromatherapy.

Other herbal therapies and dietary supplements have been advertised as cures for cancer:

- Hoxsey formulas. The Hoxsey formulas are herbal remedies for external as well as internal use. The external Hoxsey formula contains bloodroot, which was used by some Native Americans to treat cancer. The internal formula is a mixture of red clover, buckthorn, burdock, licorice root, and several other herbs. The American Cancer Society placed the Hoxsey formulas on its list of unproven methods in 1968.
- Cartilage. Both bovine (cow) and shark cartilage are available in the United States as dietary supplements. Shark cartilage is presently being studied as a cancer treatment in clinical trials approved by the FDA. It appears to slow down or stop the formation of new blood vessels (angiogenesis) in tumors in animals. As of 2001, however, it is not clear that shark cartilage is an effective anti-cancer treatment in humans.
- Coenzyme Q_{10}. Coenzyme Q_{10}, also known as vitamin Q_{10}, ubiquinone, or ubidecarenone, is a compound that occurs naturally in the human body. It appears to help cells produce energy and to stimulate the immune system. Coenzyme Q_{10} has not been investigated widely as a treatment for cancer in humans as of 2001, but it has been reported to lengthen the survival of cancer patients. It is sold in the United States as a dietary supplement.
- Mistletoe. Mistletoe (*Viscum album*) is a parasitic plant that has been shown to kill cancer cells in laboratory tests and stimulate the immune system. Although the leaves and berries are toxic to humans, mistletoe extracts are available over the counter in Europe and Asia. There is no clinical evidence that mistletoe is an effective treatment for human cancer, and mistletoe extracts have not been approved for sale in the United States.
- Pau d'arco. Pau d'arco comes from a tree in the South American rainforest. The bark is dried and used to brew a medicinal tea. Pau d'arco was investigated by the NCI for possible anti-tumor effectiveness, but the study concluded in 1974 that a dose strong enough to shrink tumors in humans would have toxic side effects. In small doses, however, pau d'arco tea does appear to stimulate the immune system. It can be purchased in the United States in health food stores.
- Essiac tea. Essiac is a mixture of herbs including burdock, slippery elm inner bark, sheep sorrel, Turkish rhubarb, watercress, red clover, and kelp. Promoters of Essiac claim that the tea strengthens the immune system, relieves pain, increases appetite, reduces tumor size, and extends survival. Some also claim that it cleanses the blood, promotes cell repair, restores energy levels, and detoxifies the body. Despite testimonials, there is no scientific evidence to support the use of this mixture for cancer treatment. NCI studies of Essiac in 1983 found no anticancer activity. However, serious side effects from these herbs are rare, and patients may benefit psychologically from the treatment.

External energy therapies

Treatments in this category are based on the belief that there are forms of energy in the universe that can be tapped for purposes of human healing. These energies, which are sometimes called "subtle energies," are thought to be present in mineral formations, plants, the earth's magnetic field, the spectrum of visible light, interpersonal contact, and certain structures or energy fields within the human body itself. Most practitioners of external energy therapies do not ask cancer patients to avoid or give up conventional treatment methods.

The most common forms of external energy therapies include:

- Crystal/gemstone healing. Crystal or gemstone healing is based on the theory that the human body is surrounded by an invisible energy field, or aura, and that the color or crystal structure of a gemstone or mineral can transmit healing energy to the body through the aura.
- Shamanism. Shamanism is the belief that certain persons (shamans) have unusual spiritual powers that can be used for healing. The shaman (who may be a woman in some traditions) acts as an intermediary between the patient and supernatural beings or powers. Native American healers are one type of shaman.
- Bach flower remedies. The 38 Bach flower remedies are tinctures of wildflowers discovered by an English homeopath in the 1920s. They are said to assist physical healing by clearing up negative emotional states or conditions.
- Light/color therapy. Light or color treatment combines the physical effects of the different wavelengths in visible light with the psychological or symbolic meanings attached to specific colors. The practitioner may suggest wearing or visualizing certain colors, or shine colored lights on specific energy points on the patient's body.

- Reiki. Reiki is a holistic approach based on Eastern concepts of universal life energy in which the practitioner holds her or his hands in symbolic patterns over the affected part of the patient's body. It is not a form of massage. Reiki can be used for self-healing as well as treating someone else.
- Therapeutic touch. Therapeutic touch resembles Reiki in that the practitioner is thought to transmit universal energy or "life force" to the patient. Instead of touching the patient directly, however, the practitioner passes his or her hands over the patient's energy field, two to four inches above the body.

Mind- and spirituality-based approaches

Mind-based or spirituality-based approaches draw on the mental and spiritual dimensions of human beings to treat the physical side effects of cancer treatment. They are related to the belief that all dimensions of a person's being should be involved in cancer treatment, and that the mind and spirit can affect or influence physical processes.

These approaches are frequently recommended by health professionals as complementary treatments that allow patients to regain a sense of personal effectiveness and active participation in their lives:

- Prayer. Prayer has been shown in over a hundred reputable double-blind clinical studies to have positive effects on anxiety, high blood pressure, headaches, heart disease, and wounds. As of 2001, NCCAM is conducting a study of the effects of prayer on **breast cancer** in African-American women.
- Meditation. Meditation is helpful in relieving stress, pain, and other side effects of cancer treatment. There are several different approaches to meditation, such as using a mantra (a sacred word or phrase), chanting, focusing on a visual image, or focusing on one's breath.
- Biofeedback. Biofeedback is a method of learning to modify certain body functions (temperature, heart rate, etc.) related to relaxation with the help of electronic monitors. Eventually, the patient can learn to control his or her relaxation responses without feedback from the machine.
- Hypnosis. Hypnosis is often recommended to lower anxiety and relieve pain. Patients can be hypnotized by a therapist or taught to hypnotize themselves. Hypnosis and biofeedback have both been shown to ease chemotherapy-related nausea and anticipatory nausea (queasiness caused by psychological triggers, such as the sight of the chemotherapy room or smell of treatment chemicals).
- Imagery and visualization. Patients are asked to picture or create an inner image that symbolizes their resistance to cancer. They might visualize their medications as a fire burning up their cancer cells, or their white blood cells as soldiers fighting the enemy.

Sensory-based therapies

Treatments in this category are often used in integrative treatment plans. They are given to help cancer patients cope with the side effects of radiation or chemotherapy, to provide positive sensory experiences, and to improve overall quality of life.

Sensory-based treatments include:

- Aromatherapy. Aromatherapy is the use of fragrances—usually the essential oils of flowers and other plant parts—to relax cancer patients or lift their spirits. The fragrant oils are used to scent oil for massage or added to bath water.
- Art therapy. Art therapy allows cancer patients to express their feelings through their creations and to find satisfaction in learning new skills or techniques. Art therapy may include painting, sculpture, making pottery, quilting, metalwork, print making, photography, or other activities.
- Journaling. Keeping a journal can aid a patient's psychological well being by providing an emotional and creative outlet. Journaling also offers an arena in which patients can sort out thoughts and concerns about their disease.
- Music therapy. Music therapy can be used to help patients relax, release feelings of sadness or anger, or participate in a group activity. It can involve making music as well as listening to it.
- Pet therapy. Pet therapy is the use of trained animals (usually cats, small dogs, birds, or rabbits) in hospital settings to provide comfort and companionship to cancer patients. Petting and talking to the animals has been shown to benefit patients psychologically and physically.

Traditional approaches

Some of the therapies in this category developed outside the European medical tradition, while the last two developed in the West during the eighteenth and nineteenth centuries:

- Native American medicine. Specific beliefs about the causes of disease vary among the five hundred tribes of Native Americans. In general, however, Native American medicine emphasizes the importance of people living in beauty, harmony, and peace with one another and with their environment. Native American healing rituals are most often used as com-

KEY TERMS

Adjunctive—Any form of therapy that is considered to help or assist a patient's primary treatment.

Alternative—A form of treatment outside mainstream medicine that is used as a cure instead of standard treatments.

Angiogenesis—The formation of blood vessels. Shark cartilage is undergoing tests on its effects on angiogenesis in tumors.

Anorexia—Loss of appetite. Anorexia is a common side effect of chemotherapy.

Aura—The field of subtle energy that surrounds the human body, according to external energy therapists.

Biologics—Drugs or other medical products made from biological sources.

Cachexia—The wasting away of body tissue.

Complementary—Any form of treatment outside the mainstream that is not considered a cure but is given to ease symptoms or contribute to general well-being.

Detoxification—Ridding the body of digestive wastes considered toxic through fasting, drinking large quantities of juice, or colonic irrigation.

Holistic—Any approach to health care that emphasizes the patient's total well-being, including psychological and spiritual as well as physical aspects.

Integrative—An approach to cancer treatment that combines mainstream therapies with one or more complementary therapies.

Investigational—A drug or therapy that is approved for use in clinical trials but not for regular treatment of patients.

Mantra—A sacred word or phrase, used in some forms of meditation to deepen the meditative state.

Quackery—A fraudulent form of treatment or therapy.

Vegan—A vegetarian who omits all animal products, including eggs and milk, from their diet.

plementary treatments within integrative treatment plans.

- Ayurveda. Ayurveda is the traditional medical system of India. It emphasizes identifying a person's physical and psychological constitution as part of the healing process. Treatments include dietary recommendations and herbal or mineral remedies.
- Traditional Chinese medicine (TCM). TCM includes five major forms of treatment: diet, exercise, acupuncture, massage, and traditional herbal remedies. It regards human health as resulting from balancing the various vital energies within the human body and keeping the body in harmony with its external environment. As of 2001, the Center for Cancer Complementary Medicine at Johns Hopkins is conducting two studies of Chinese herbal remedies.
- Homeopathy. Homeopathy is a system of treating disease with extremely small doses of substances that would produce symptoms in a healthy person similar to those of the disease being treated. For example, a homeopathic practitioner might give a feverish patient belladonna, which can cause **fever** in a healthy person.
- Naturopathy. Naturopathy is an approach to healing that rejects surgery and synthetic drugs. Naturopaths recommend vitamin supplements, natural herbal remedies, diets, and fasting to assist the body's natural healing processes.

Special concerns

Because complementary and alternative therapies vary so widely in their underlying assumptions, their claims to effectiveness, their licensing standards for practitioners, and the materials and equipment involved in their use, patients should talk to their doctor before beginning any complementary or alternative form of treatment. Patients should also investigate said treatments and the practitioner's level of experience in this area.

Surgery

Cancer patients who have had recent surgery should consult their doctor before starting yoga, t'ai chi, or any other form of movement therapy. In addition, Swedish massage and certain forms of deep tissue massage are not suitable for patients who have not fully recovered from surgery.

Clinical trials

Patients who are interested in a specific complementary or alternative therapy may wish to participate in a study of that treatment. Information about CAM trials can be obtained from the NCI's CancerNet at <http://www.cancernet.nci.nih.gov/cam>.

Fraudulent treatments

False claims about a treatment, such as stating that it cures or prevents cancer when it is known to be useless, are sometimes referred to as "quackery." Several groups and organizations can help patients evaluate questionable therapies.

Treatment decisions

Patients considering CAM therapies should ask their doctor:

- What does the treatment claim to do? Cure cancer? Increase the effectiveness of standard treatments? Or relieve symptoms or side effects?
- How is the practitioner licensed or credentialed? For example, there are licensing boards in most states for massage therapists, acupuncturists, practitioners of Chinese medicine, yoga instructors, and homeopaths.
- Is the treatment based on specific theories about the causes of cancer? How are these theories regarded by mainstream health professionals?
- Is the treatment associated with specific types of cancer, such as cancers of the digestive tract or the nervous system?
- Does the treatment have any restrictions or side effects of its own?
- Is the treatment recommended for other diseases or conditions, or only for cancer?
- How is the treatment advertised or promoted? In medical journals, mainstream health publications, the mass media, or only in "New Age" or special-interest magazines?

Patients should look for "red flags" that may indicate that a treatment is fraudulent:

- The treatment is unusually expensive.
- It is based on unproven or discredited theories.
- It claims to be a "secret" offered by only a few providers.
- Patients must go outside the United States or Canada for the treatment.
- Patients are told not to use standard cancer treatments.
- The treatment lacks any connection to reputable licensing bodies, medical schools, research institutions, or cancer organizations.

Resources

BOOKS

American Cancer Society. *The American Cancer Society's Guide to Complementary and Alternative Cancer Methods*. New York: American Cancer Society, 2000.

National Cancer Institute of the National Institutes of Health. *Chemotherapy and You: A Guide to Self-Help During Cancer Treatment*. NIH Publication #99-1136. Can be downloaded from <http://cancernet.nci.nih.gov>.

ORGANIZATIONS

American Academy of Medical Acupuncture. (800) 521-2262.

American Association of Naturopathic Physicians. 601 Valley St., Suite 105, Seattle, WA 98109. (206) 298-0126. Fax: (206) 298-0129. <http://www.naturopathic.org>.

American Botanical Council. <http://www.herbalgram.org>.

American Cancer Society (ACS). 1599 Clifton Road, NE, Atlanta, GA 30329. (404) 320-3333 or (800) ACS-2345. Fax: (404) 329-7530. <http://www.cancer.org>.

American Foundation of Traditional Chinese Medicine (AFTCM). 505 Beach Street, San Francisco, CA 94133. (415) 776-0502. Fax: (415) 392-7003. E-mail: aftcm@earthlink.net.

American Herbal Products Association. 8484 Georgia Ave., Suite 370, Silver Spring, MD 20910. (301) 588-1174. <http://www.ahpa.org>.

American Indian Science and Engineering Society (AISES). 5661 Airport Blvd., Boulder, CO 80301-2339. (303) 939-0023. Fax: (303) 939-8150. E-mail: aisehq@spot.colorado.edu. <http://www.colorado.edu/aises>.

Consumer Reports Health Letter. P.O. Box 52145, Boulder, CO 80321.

Delta Society (pet therapy). <http://www.deltasociety.org>.

National Cancer Institute, Office of Cancer Communications. 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. TTY: (800) 332-8615. Email: cancermail@cips.nci.nih.gov. <http://www.nci.nih.gov>.

National Center for Homeopathy (NCH). 801 North Fairfax St., Suite 306, Alexandria, VA 22314. (703) 548-7790. Fax: (703) 548-7792.

National Certification Board for Therapeutic Massage and Bodywork. 8201 Greensboro Drive, Suite 300, McLean, VA 22102. (703) 610-9015.

National Council Against Health Fraud. P.O. Box 1276, Loma Linda, CA 92354.

NIH National Center for Complementary and Alternative Medicine (NCCAM) Clearinghouse. P. O. Box 8218, Silver Spring, MD 20907-8218. TTY/TDY: (888) 644-6226. Fax: (301) 495-4957. <http://www.nccam.nih.gov>.

NIH Office of Dietary Supplements. Building 31, Room 1B25, 31 Center Drive, MSC 2086. Bethesda, MD 20892-2086. (301) 435-2920. Fax: (301) 480-1845. Web site: http://odp.od.nih.gov/ods.

Office of Cancer Complementary & Alternative Medicine of the National Cancer Institute (OCCAM). Email: ncioccam1-r@mail.nih.gov. <http://www.occam.nci.nih.gov>.

Quackwatch. <http://www.quackwatch.com>.

OTHER

Cancer Supportive Care Programs. [cited June 21, 2001]. <http://www.cancersupportivecare.com>. Provides information about pain control, nutrition, and other aspects of supportive care for cancer patients.

The Wellness Community. [cited June 21, 2001]. <http://www.wellness-community.org>. Offers support groups, stress reduction workshops, exercise programs, social events, and nutritional counseling for cancer patients and their families.

Rebecca J. Frey, Ph.D.

Computerized axial tomography *see* **Computed tomography**

Computed tomography

Definition

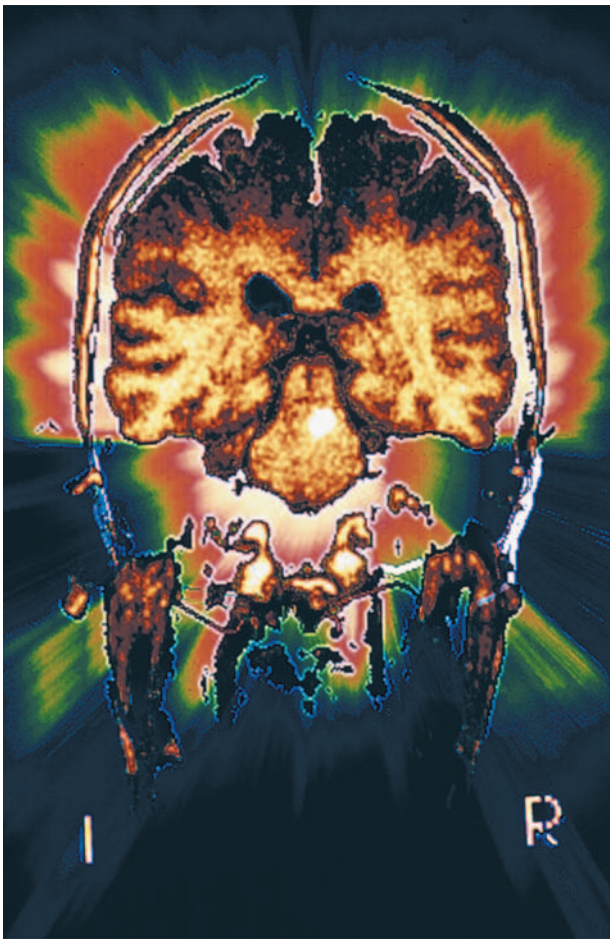
Computed tomography (CT) scanning is a valuable diagnostic tool that provides physicians with views of internal body structures. During a CT scan, multiple x rays are passed through the body, producing cross-sectional images, or "slices," on a cathode-ray tube (CRT), a device resembling a television screen. These images can then be preserved on film for examination.

Purpose

CT scans are used to image bone, soft tissues, and air. Since the 1990s, CT equipment has become more affordable and available. CT scans have become the imaging exam of choice for the diagnoses of most solid tumors. Because the computerized image is sharp, focused, and three-dimensional, many structures can be better differentiated than on standard x rays.

Common indications for CT scans include:

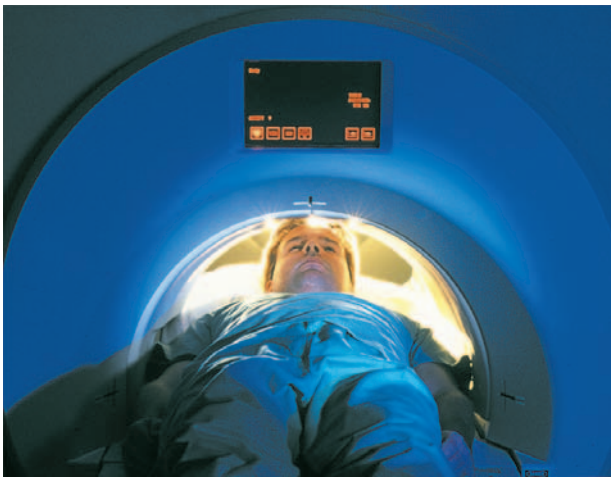
- Sinus studies. The CT scan can show details of sinusitis, bone fractures, and the presence of bony tumor involvement. Physicians may order a CT scan of the sinuses to provide an accurate map for surgery.
- Brain studies. Brain CT scans can detect hematomas, tumors, strokes, aneurysms, and degenerative or infected brain tissue. The introduction of CT scanning, especially spiral CT, has helped reduce the need for more invasive procedures such as cerebral angiography.
- Body scans. CT scans of the chest, abdomen, spine, and extremities can detect the presence of tumors, enlarged lymph nodes, abnormal collection of fluid, and vertebral disc disease. These scans can also be helpful in evaluating the extent of bone breakdown in osteoporosis.
- Heart and aorta scans. CT scans can focus on the thoracic or abdominal aorta to locate aneurysms and other possible aortic diseases. A newer type of CT scan, called electron beam CT, can be used to detect calcium buildup in arteries. Because it is a new technology, it is not yet widely used and its indications are not yet well-defined.
- Chest scans. CT scans of the chest are useful in distinguishing tumors and in detailing accumulation of fluid in chest infections.



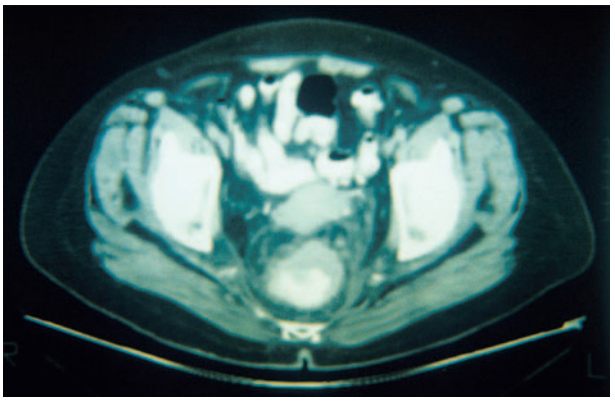
A computed tomography (CT) scan, colorized, of the human brain. *(Custom Medical Stock Photo. Reproduced by permission.)*

Precautions

Pregnant women or those who could possibly be pregnant should not have a CT scan, particularly a full body or abdominal scan, unless the diagnostic benefits outweigh the



Patient passes into a CT (computed tomography or CAT) scanner. *(Copyright Volker Steger/Science Photo Library, Science Source/Photo Researchers, Inc. Reproduced by permission.)*



CT scan (without color added) of cancer of the rectum. *(Custom Medical Stock Photo. Reproduced by permission.)*

risks. If the exam is necessary for obstetric purposes, technologists are instructed not to repeat films if there are errors. Pregnant patients receiving a CT scan or any **x ray** exam away from the abdominal area may be protected by a lead apron; most radiation, known as scatter, travels through the body, however, and is not blocked by the apron.

Contrast agents are often used in CT exams, though some types of tumors are better seen without it. Patients should discuss the use of contrast agents with their doctor, and should be asked to sign a consent form prior to the administration of contrast. One of the common contrast agents, iodine, can cause allergic reactions. Patients who are known to be allergic to iodine or shellfish should inform the physician prior to the CT scan; a combination of medications can be given to such patients before the scan to prevent or minimize the reaction. Contrast agents may also put patients with diabetes at risk of kidney failure, particularly those taking the medication glucophage.

Description

Computed tomography, also called CT scan, CAT scan, or computerized axial tomography, is a combination of focused x-ray beams and the computerized production of an image. Introduced in the early 1970s, this radiologic procedure has advanced rapidly and is now widely used, sometimes in the place of standard x rays.

CT equipment

A CT scan may be performed in a hospital or outpatient imaging center. Although the equipment looks large and intimidating, it is very sophisticated and fairly comfortable. The patient is asked to lie on a gantry, or narrow table, that slides into the center of the scanner. The scanner looks like a doughnut and is round in the middle, which allows the x-ray beam to rotate around the patient. The scanner section may also be tilted slightly to allow for certain cross-sectional angles.

CT procedure

The gantry moves very slightly as the precise adjustments for each sectional image are made. A technologist watches the procedure from a window and views the images on a computer screen. Generally, patients are alone during the procedure, though exceptions are sometimes made for pediatric patients. Communication is possible via an intercom system.

It is essential that the patient lie very still during the procedure to prevent motion blurring. In some studies, such as chest CTs, the patient will be asked to hold his or her breath during image capture.

Following the procedure, films of the images are usually printed for the radiologist and referring physician to review. A radiologist can also interpret CT exams on the computer screen. The procedure time will vary in length depending on the area being imaged. Average study times are from 30 to 60 minutes. Some patients may be concerned about claustrophobia but the width of the "doughnut" portion of the scanner is such that many patients can be reassured of openness. Doctors may consider giving sedatives to patients who have severe claustrophobia or difficulty lying still.

The CT image

While traditional x-ray machines image organs in two dimensions, often resulting in organs in the front of the body being superimposed over those in the back, CT

KEY TERMS

Aneurysm—The bulging of the blood vessel wall. Aortic aneurysms are the most dangerous. Aneurysms can break and cause bleeding.

Contrast (agent, medium)—A substance injected into the body that illuminates certain structures that would otherwise be hard to see on the radiograph (film).

Gantry—A name for the couch or table used in a CT scan. The patient lies on the gantry while it slides into the x-ray scanner.

Hematoma—A collection of blood that has escaped from the vessels. It may clot and harden, causing pain to the patient.

Metastasis—Secondary cancer, or cancer that has spread from one body organ or tissue to another.

Radiologist—A medical doctor specially trained in radiology (x ray) interpretation and its use in the diagnosis of disease and injury.

Spiral CT—Also referred to as helical CT, this method allows for continuous 360-degree x-ray image capture.

Thoracic—Refers to the chest area. The thorax runs between the abdomen and neck and is encased in the ribs.

scans allow for a more three-dimensional effect. CT images can be likened to slices in a loaf of bread. Precise sections of the body can be located and imaged as cross-sectional views. The screen before the technologist shows a computer's analysis of each section detected by the x-ray beam. Thus, various densities of tissue can be easily distinguished.

Contrast agents

Contrast agents are often used in CT exams and in other radiology procedures to illuminate certain details of anatomy more clearly. Some contrasts are natural, such as air or water. A water-based contrast agent is sometimes administered for specific diagnostic purposes. Barium sulfate is commonly used in gastroenterology procedures. The patient may drink this contrast or receive it in an enema. Oral or rectal contrast is usually given when examining the abdomen or cells, but not when scanning the brain or chest. Iodine is the most widely used intravenous contrast agent and is given through an intravenous needle.

If contrast agents are used in the CT exam, these will be administered several minutes before the study begins. Patients undergoing abdominal CT may be asked to drink a contrast medium. Some patients may experience a salty taste, flushing of the face, warmth or slight nausea, or hives from an intravenous contrast injection. Technologists and radiologists have the equipment and training to help patients through these minor reactions and to handle more severe reactions. Severe reactions to contrast are rare, but do occur.

Newer types of CT scans

The spiral CT scan, also called a helical CT, is a newer version of CT. This type of scan is continuous in motion and allows for the continuous re-creation of images. For example, traditional CT allows the technologist to take slices at very small and precise intervals one after the other. Spiral CT allows for a continuous flow of images, without stopping the scanner to move to the next image slice. A major advantage of spiral CT is the ability to reconstruct images anywhere along the length of the study area. Because the procedure is faster, patients are required to lie still for shorter periods of time. The ability to image contrast more rapidly after it is injected, when it is at its highest level, is another advantage of spiral CT's high speed.

Electron beam CT scans are another newer type of CT technology that can be used to detect calcium buildup in arteries. These calcium deposits are potential risk factors for coronary artery disease. Electron beam CT scans take pictures much more quickly than conventional CTs, and are therefore better able to produce clear images of the heart as it pumps blood. Because it is a newer and expensive test, electron beam CT scanning is not widely used.

Some facilities will have spiral, electron, and conventional CT available. Although spiral is more advantageous for many applications, conventional CT is still a superior and precise method for imaging many tissues and structures. The physician will evaluate which type of CT works best for the specific exam purpose.

Preparation

If a contrast medium is administered, the patient may be asked to fast for about four to six hours prior to the procedure. Patients will usually be given a gown (like a typical hospital gown) to be worn during the procedure. All metal and jewelry should be removed to avoid artifacts on the film. Depending on the type of study, patients may also be required to remove dentures.

Aftercare

Generally, no aftercare is required following a CT scan. Immediately following the exam, the technologist will continue to watch the patient for possible adverse contrast reactions. Patients are instructed to advise the technologist of any symptoms, particularly respiratory difficulty. The site of contrast injection will be bandaged and may feel tender following the exam.

Risks

Radiation exposure from a CT scan is similar to, though higher than, that of a conventional x ray. Although this is a risk to pregnant women, the risk for other adults is minimal and should produce no effects. Severe contrast reactions are rare, but they are a risk of many CT procedures.

Normal results

Normal findings on a CT exam show bone, the most dense tissue, as white areas. Tissues and fat will show as various shades of gray, and fluids will be gray or black. Air will also look black. Intravenous, oral, and rectal contrast appear as white areas. The radiologist can determine if tissues and organs appear normal by the sensitivity of the gray shadows.

Abnormal results

Abnormal results may show different characteristics of tissues within organs. Accumulations of blood or other fluids where they do not belong may be detected. Radiologists can differentiate among types of tumors throughout the body by viewing details of their makeup.

Sinus studies

The increasing availability and lowered cost of CT scanning has lead to its increased use in sinus studies, either as a replacement for a sinus x ray or as a follow-up to an abnormal sinus radiograph. The sensitivity of CT allows for the location of areas of sinus infection, particularly chronic infection. Sinus tumors will show as shades of gray indicating the difference in their density from that of normal tissues in the area.

Brain studies

The precise differences in density allowed by CT scan can clearly show tumors, strokes, or lesions in the brain area as altered densities. These lighter or darker areas on the image may indicate a tumor or hematoma within the brain and skull area. Different types of tumors can be identified by the presence of edema, by the tissue's density, or by studying blood vessel location and activity. The speed and convenience of CT often allows for detection of hemorrhage before symptoms even occur.

QUESTIONS TO ASK THE DOCTOR

- Why is a CT scan recommended in my case?
- What are the benefits associated with this procedure?
- What are the risks associated with this procedure?
- How do I prepare for the CT scan?
- When will I know the results?

Body scans

The body CT scan can identify abnormal body structures and organs. A CT scan may indicate tumors or cysts, enlarged lymph nodes, abnormal collections of fluids, blood or fat, or cancer **metastasis**. Tumors resulting from metastasis are different in makeup than primary (original) tumors.

Chest scans

In addition to those findings which may indicate aortic aneurysms, chest CT studies can show other problems in the heart and lungs, and distinguish between an aortic aneurysm and a tumor adjacent to the aorta. CT will not only show differences between air, water, tissues and bone, but will also assign numerical values to the various densities. Coin-sized lesions in the lungs may be indicative of tuberculosis or tumors. CT will help distinguish among the two. Enlarged lymph nodes in the chest area may indicate **Hodgkin's disease**.

Resources

BOOKS

Abeloff, M. *Clinical Oncology*. 2nd ed. Orlando, Florida: Churchill Livingstone, Inc., 2000.

PERIODICALS

Holbert, J. M. "Role of Spiral Computed Tomography in the Diagnosis of Pulmonary Embolism in the Emergency Department." *Annals of Emergency Medicine* May 1999: 520-28.

Teresa G. Odle

Corticosteroids

Definition

Corticosteroids are a group of related drugs used in cancer treatment to reduce the growth of tumors, stimulate the appetite, and treat skin rashes, **nausea and vomiting**, allergic reactions, inflammation, accumulation of fluid in the brain, and autoimmune disease.

Purpose

Corticosteroids have broad use in cancer treatment. Some are used to treat adult leukemias, adult lymphomas, acute childhood leukemia, **multiple myeloma**, and advanced **prostate cancer**. Others are used in creams to treat skin rashes from **radiation therapy**. Corticosteroids are also used to reduce swelling, especially in the brain and spinal column, reduce nausea and vomiting, and improve appetite.

Description

Corticosteroids occur naturally in the body. They are produced by the cortex of the adrenal glands, a small, pea-sized pair of glands that are located in the lower back, just above the kidney. Some corticosteroids regulate fluid balance in the body. Others influence fat and sugar (glucose) usage. Corticosteroids are chemically related to the sex hormones estrogen and **testosterone**.

Many different corticosteroids are produced artificially to use as drugs. They are administered as creams, tablets, liquids, or intravenously (or injection directly into a vein). Many people are already familiar with hydrocortisone, a corticosteroid found in low doses in over-the-counter creams.

The most common corticosteroids used in cancer treatment are:

- dexamethasone (Decadron)
- hydrocortisone
- methylprednisolone (Medrol)
- prednisone
- cortisone
- betamethasone
- prednisoloneThere are many trade names for drugs containing these corticosteroids.

Recommended dosage

Corticosteroids come in tablets, liquids, intravenous solutions, and creams. Because of their wide variety of uses and forms, there is no standard recommended dose. Dosage is individualized, and depends on the type of cancer, the patient's body weight and general health, the goal of the treatment, the other drugs being given, and the way a patient's cancer responds to the drug. Corticosteroids should be stored away from heat.

KEY TERMS

Autoimmune disease—An illness occurring when the body's tissues are attacked by its own immune system

Intravenous injection—Injection directly into the vein

Precautions

People taking corticosteroids may want to go on a low-salt, high-potassium diet in order to reduce water retention. They may also want to watch their calorie intake unless corticosteroids are being given to improve appetite. Patients taking large doses of corticosteroids are more susceptible to infection and should try to avoid contact with crowds or any individuals that may have an infection. Patients should seek immediate medical advice if they are exposed to chicken pox or measles.

Side effects

Corticosteroids have several side effects. Not every side effect is seen in every patient. The most serious, although rare, side effect is an allergic reaction to corticosteroids when given intravenously (IV). Other side effects can include:

- salt and water retention
- excessive potassium loss
- high blood pressure
- other fluid and electrolyte imbalances
- loss of muscle tissue
- loss of bone strength (osteoporosis)
- easily fractured bones
- heartburn and ulcers
- thin, fragile skin
- slow wound healing
- skin rashes
- masking of infection
- convulsions
- headache
- dizziness

- reproductive irregularities
- strong mood changes
- changes in the functioning of the adrenal gland
- increased pressure in the eye
- glaucoma, cataracts, and blindness (rare)
- nausea
- fatigue
- increased appetite
- weight gain
- increased urination

Interactions

Many drugs interact with nonprescription (over-the-counter) drugs and herbal remedies. Patients should always tell their health care providers about these remedies, as well as any prescription drugs they are taking. Patients should also notify their physician if they are on a special diet.

Corticosteroids can also interact with anticoagulants (blood thinners such as Coumadin), **cyclosporine**, phenobarbitol, and antidepressants.

Tish Davidson, A.M.

Coughing up blood *see* **Hemoptysis**

Craniopharyngioma

Definition

Craniopharyngioma is a cancer which arises in the pituitary gland, in tissue originally found in the embryo. One of the most common childhood brain cancers, it is also sometimes called a Rathke's pouch tumor or a suprasellar cyst.

Description

Craniopharyngioma is the second most common type of childhood brain tumor, accounting for almost 10% of all brain tumors in children. This cancer has very little tendency to spread to other parts of the body. It readily invades local tissues, however, and since it occurs deep within the brain, invasion of local tissues alone can result in serious illness or even death.

The pituitary gland produces many hormones that play critical roles in the development and regulation of the body. Because this cancer arises in the pituitary gland, it often results in deficiencies of the various hormones that the pituitary gland produces. The tumor can be either solid or cystic or mixed, and most (up to 90%) of craniopharyngiomas contain calcium deposits, an indication of diseased tissue readily observable on x rays.

Demographics

The large majority of craniopharyngiomas are childhood tumors. The median age at diagnosis is eight years; peak incidence is between the ages of six and eleven. Almost 70% of all craniopharyngiomas occur before the age of 20, although a small peak occurs after the age of 50. Diagnosis before the age of two is very rare. Girls and boys and all races are affected equally.

Causes and symptoms

The cause of craniopharyngioma is not really understood, although it is believed to be primarily a congenital illness. Nests of embryonic cells exist in a part of the pituitary gland known as Rathke's pouch. In craniopharyngioma, these nests appear to contain cancerous cells which, over time, multiply and become a tumor.

The symptoms of craniopharyngioma can be divided into two categories. Some are nonspecific symptoms which occur because of increased pressure within the skull; some result from deficiencies of the hormones that the pituitary gland normally produces. Any individual patient may have various combinations of symptoms and both the number of symptoms and the severity of the symptoms typically increase over time. Nonspecific symptoms of increased intracranial pressure include:

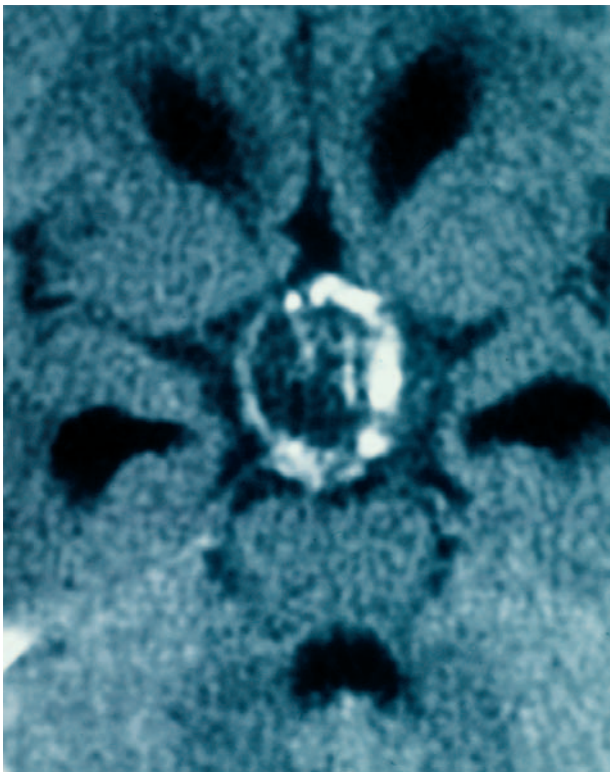
- headache
- visual disturbances
- irritability
- personality changes
- mental disturbances

Symptoms that can result from hormone deficiencies include:

- diabetes
- growth retardation
- sexual dysfunction (in adults)

Diagnosis

Most patients seek medical attention because of headaches or visual disturbances, failure to match normal growth patterns (due to a deficiency of growth



Magnetic resonance image (MRI) of a craniopharyngioma brain tumor. *(Custom Medical Stock Photo. Reproduced by permission.)*

hormone), or symptoms of diabetes. If (after other causes of symptoms are ruled out) a craniopharyngioma is suspected, usually some kind of imaging technique is performed. Traditional x rays reveal an enlargement of the space at the base of the skull where the tumor is typically found, and will also show calcification of cancerous cells. **Computed tomography** (CT scan or CAT scan) may show calcification that does not show up on x rays and also shows whether the tumor is cystic or solid in nature. **Magnetic resonance imaging** (MRI) can show how much the tumor has invaded the surrounding tissues.

Often the amounts of pituitary hormones in the blood are measured as well. Measurements may be made of gonadatropins (hormones which regulate reproduction), thyrotropin (a hormone that regulates the thyroid gland), growth hormones (regulates growth), corticotropin (a hormone that regulates carbohydrate metabolism, vasopressin (a hormone that regulates water retention), or prolactin (a hormone that regulates milk production in mothers of infants).

Treatment team

As the understanding of cancer grows and new treatment approaches are developed, the complexity of cancer treatment also increases. Today, a multidisciplinary approach to cancer treatment is considered necessary for effective patient care. Since craniopharyngioma is a neuroendocrine tumor that occurs deep in the brain and mainly in children, optimal treatment requires a particularly complex and sophisticated team of health professionals. The types of people who may be involved in treating or caring for a patient with craniopharyngioma and their family typically include oncologists (pediatric), pathologists (neuropathologists), radiation oncologists, radiation technicians, psychiatrists, oncology social workers, nutritionists, home health care providers, endocrinologists, rehabilitative specialists, and neurosurgeons. The surgeon, specifically, should be a pediatric neurosurgeon, as these specialists have been shown to provide better long-term outcomes than general neurosurgeons.

Clinical staging, treatments, and prognosis

Standard treatment for craniopharyngioma consists of surgical removal of as much of the tumor as is readily accessible, followed by **radiation therapy**. Although total removal of the tumor yields the best odds of survival, the location in which this cancer occurs (and the fact that these tumors are typically covered by a thick membrane that adheres tightly to surrounding tissues) can make total removal difficult. Attempts to remove the tumor completely, therefore, often result in significant and unacceptable side effects. A better quality of life, and therefore better overall outcome, is obtained through partial removal of the tumor followed by radiation therapy. This is now generally accepted as the best treatment approach.

Chemotherapy is not routinely used for treatment of craniopharyngioma, although some medications are commonly used to treat symptoms. Drugs that decrease inflammation and reduce the probability of convulsions may be given preoperatively to make surgical removal of the tumor safer. Hormone replacement therapy may be necessary if the cancer, occurring in the pituitary gland, causes serious hormone deficiency problems.

Therapies that are not routinely used but have shown some promise include internal placement of radioactive material and improvements in surgical techniques, including stereotactic surgery, which utilizes a radioactive ‘‘gamma knife’’ for excision of the tumor.

Since this type of cancer does not demonstrate a tendency to spread to remote areas of the body, staging or grading systems are not usually used. Factors that improve survival are complete removal of the tumor (although this often results in greatly decreased quality of life), the size of the tumor at diagnosis, a cystic rather

than solid nature of the tumor, and an age of at least five years old at diagnosis. Unfortunately, most patients who survive have significant remaining illness, and predicting how much function may be lost is as important in this cancer as prognosis of survival. It is important to remember, especially with regards to extent of functional capacity to be expected, that the physician's prognosis is only an educated guess, and that positive thinking can contribute significantly to a better quality of life.

Alternative and complementary therapies

Alternative and complementary therapies are treatments which are not traditional, first-line therapies like surgery, chemotherapy and radiation. Complementary therapies are those that are meant to supplement traditional therapies and usually have the objective of relieving symptoms or helping cancer patients cope with the disease or traditional treatments. Alternative therapies are nontraditional treatments which are chosen instead of traditional treatments in an attempt to cure the disease. Alternative therapies have typically not been proven to be effective in the same way that traditional drugs are evaluated, in studies called **clinical trials**, and are usually not recommended for use with children.

Common complementary therapies that may be employed by cancer patients include aromatherapy, art therapy, massage, meditation, music therapy, prayer, t'ai chi, and yoga or other forms of exercise, which reduce anxiety and can increase a patient's feeling of well-being. Many patients also take high doses of **vitamins** and other nutritional supplements, especially A, C, E, and selenium, which are thought to act as **antioxidants**. Any physical activities or nutritional supplements (especially when treating a child) should be discussed with then patient's physician.

Numerous alternative therapies exist in cancer treatment. Special caution must be used, however, when considering alternative therapies for children's cancers. Although alternative treatments, by definition, have not been proven effective by scientific methods, some brain tumor patients believe that the use of alternative therapies has been beneficial. Some alternate therapies include:

- Laetrile, a product of apricot seeds, contains a form of cyanide that proponents believe may be released by tumor enzymes and act to kill cancerous cells. Laetrile is not approved by the Food and Drug Administration for use in the United States. The National Cancer Institute sponsored two studies of laetrile in the late 1970s and early 1980s, but concluded after the second study that no additional research was necessary.
- Vitamin E, melatonin, aloe vera, and a compound called beta-1,3-glucan are reported to stimulate the immune system. Some practitioners believe that natural substances like garlic, ginger, and shark cartilage shrink tumors, although how they are supposed to work is not really defined.
- Antineoplastons are believed by some to be another alternative approach to a cancer cure. Antineoplastons are small proteins which may act as molecular messengers and which may be absent from the urine and blood of many cancer patients. The therapy is based on the idea that replacing these proteins may have beneficial effects. However, the National Cancer Institute proposed phase II clinical trials, and protocols were developed, but the trials never got underway on a large scale because of lack of patient participation. The National Cancer Institute draws no definitive conclusions about the treatment's effectiveness due to lack of clinical trials.

Coping with cancer treatment

Children have special needs when coping with treatment, depending on their age. Some comprehensive resources are available about how families can cope with cancer diagnoses, but some coping strategies are summarized here. Very young children need affection, soothing, time to play, reassurances, while toddlers have these same needs, but also may need to be taught how to express their anger or frustration, and simple explanations about what is happening. School-age children may enjoy a little more involvement in their treatment plan, and will need empathy about missing school and activities. They may benefit from drawing or keeping a journal, communicating with friends, and, if possible, a little physical activity each day. Adolescents have similar needs, but also may want to keep some thoughts and feelings private, and also may have more complex spiritual concerns along with feelings of anger and frustration. The siblings and parents of the child with cancer will have needs and concerns and will need to adopt coping strategies as well. The patient's treatment team can help point the family to helpful resources.

Treatment of craniopharyngioma commonly includes surgery and radiation therapy. Although the use of radiation therapy in addition to surgery has improved the quality of life for craniopharyngioma patients, treatments unavoidably result in damage to some healthy tissues and other undesirable side effects.

Fatigue is a very common side effect of radiation therapy. Patients should expect to be very sleepy and therefore to cut back on activities, allowing plenty of time for resting and letting the body heal. It is also important to try maintain a well-balanced,nutritious diet. Patients should avoid as much extra stress as possible

KEY TERMS

Congenital—Existing at birth.

Cystic tumor—A tumor that consists of a sac filled with fluid.

Solid tumor—A tumor that consists of tissue.

Neuroendocrine—Relating to nerves and glands that produce hormones.

Stereotactic surgery—Surgery that used sophisticated methods of imaging internal organs in order to make the most precise surgical incisions.

Monoclonal antibodies—Antibodies produced in bulk that act against a single target.

Liposomes—An artificially produced, microscopic sphere, consisting of a drug surrounded by cell membrane, used to help drugs get into target cells.

QUESTIONS TO ASK THE DOCTOR

- Can you explain what kind of cancer I have?
- Can you show me where my tumor is located?
- How was this cancer diagnosed?
- What is my prognosis? What limitations will I have?
- What treatments are we going to pursue? What goals will these treatments have? What happens if these don't work?
- Are there any alternatives to these treatments?
- Do you have experience in treating this type of cancer?
- Is there anything I can do to optimize treatment? Are there any particular side effects I should expect?
- Are there complementary therapies that you would recommend? Any other things that would help me cope with the diagnosis or treatment?
- Would I benefit from radiosurgery or other new surgical techniques? Can you provide that option?
- Are there any clinical trials that you would recommend?

and should limit visitors, if needed, to avoid being overtired.

Another problem for those undergoing radiation therapy is dry, sore skin in the area being treated. (Radiation does not hurt during treatment and does not make the person radioactive.) Skin in the treatment area is essentially "burned" and may blister and peel, becoming painful. Patients with fair skin or those who have undergone previous chemotherapy have a greater risk of more serious reactions. Dry, itchy or sore skin is temporary, but skin in the treatment area may remain more sensitive to sun exposure, so a good sunscreen should be used whenever affected skin is exposed to sunlight.

Radiation therapy requires a substantial level of commitment from the patient in terms of time and emotional energy. Fear and anxiety are major factors in coping with cancer in general and these cancer treatments specifically. The feelings are completely normal. Some patients find that concentrating on restful, pleasurable activities like hobbies, prayer, or meditation is helpful in decreasing negative emotions. It is also very important that patients have people to whom they can express their fears and other negative emotions. If friends or family members are unable to provide this to patients, support groups may help to provide an environment where fears can be freely expressed and understood.

Clinical trials

Although numerous clinical trials are in progress which evaluate treatments for childhood brain tumors, few of these are specifically concerned with craniopharyngioma. Most clinical trials for childhood brain tumors are evaluating new medications or new chemotherapy combinations. Although some of these may prove effective against craniopharyngiomas, chemotherapy at this time is not considered an appropriate approach to treatment of this disease. Some new therapies with potential value for cranipharyngioma patients include new forms of drug delivery, including liposomes, and immune-based therapies like **monoclonal antibodies**. In addition, new refinements of surgical techniques, including MRI-assisted surgery and stereotactic surgery, including the bloodless "gamma knife" surgery, are being evaluated. A clinical trial evaluating a pharmaceutical therapy for a common side effect of surgical treatment of craniopharygioma, hypothalmic obesity, is ongoing.

Prevention

Craniopharyngioma is believed to be a congenital disease, and there is no known way to prevent this cancer.

Special concerns

This tumor is characterized by various diseases related to hormone deficiencies which may arise as the

result of the tumor itself or as the result of either surgical or radiation therapy. The tumor may cause problems related to hormone deficiencies, especially diabetes or growth retardation, and these are often the reason that medical attention is first sought. Craniopharyngioma patients may also experience sleep disorders, changes in personality, and mental disturbances. In addition, treatment for craniopharyngioma can create a condition called hypothalmic obesity, in which a patient steadily gains weight although eating patterns may not have changed. Although many of these problems may significantly improve with time, care of a family member with a brain tumor is a significantly stressful experience for caregivers, which creates a huge strain on normal family life.

As mentioned, **childhood cancers** create unique concerns for the children diagnosed and their families. Parents and siblings, as well as the cancer patient, all have emotional issues to address, in addition to everyday concerns, such as social development, friends, and school. Hospital staff and social workers can help direct a family to useful resources for support. Support groups for craniopharyngioma patients and for parents of craniopharyngioma patients offer patients and parents a place to discuss their fears and concerns with other people who have been impacted by this disease.

Resources

BOOKS

Abeloff, editor. *Clinical Oncology*. New York: Churchill Livingstone.

Buckman, R. *What You Really Need to Know About Cancer*. Baltimore: Johns Hopkins University Press, 1999.

PERIODICALS

Lafferty, A. R. "Pituitary Tumors in Children and Adolescents." *Journal of Clinical Endocrinology and Metabolism* 84 (December 1999): 4317-4322.

ORGANIZATIONS

American Cancer Society. 1599 Clifton Road, NE, Atlanta, GA 30329-4251. (800)586-4872 <http://www.cancer.org>.

Candlelighter Childhood Cancer Foundation. 3910 Warner St., Kensington, MD 20895. 1-800-366-2223.<http://www.candlelighters.org>.

Childhood Brain Tumor Foundation. 20312 Watkins Meadow Drive, Germantown, MD 20867. (301)515-2900. <http://www.childhoodbraintumor.org>.

National Cancer Institute. 9000 Rockville Pike, Bethesda, Maryland, 20892. (800)422-6237. <http://www.nci.nih.gov>.

National Children's Cancer Society, Suite 600, 1015 Locust St. St. Louis, MO 63101. 1-800-532-6459. <http://www.children-cancer.com>.

The Wellness Community. 10921 Reed Harman Highway, Cincinnati, Ohio, 45242 (888)793-9355.

Wendy Wippel, M.Sc.

Craniosynostosis

Definition

Craniosynostosis is a birth defect of the brain in which the cranial sutures (the fibrous joints between the bones of the skull) in the skull of an infant close too early, causing problems with normal brain and skull growth. Premature closure of the sutures may cause the skull or facial bones to change from a normal, symmetrical appearance to an abnormal, asymmetrical appearance and may also cause the pressure inside of the head to increase.

Description

The skull of an infant is made up of five free-floating bones separated by cranial sutures, which allows the infant to pass through the birth canal. The five bones are: the occipital bone, in the back portion of the skull, the two parietal bones, on either side of the skull, and two frontal bones, on the front portion of the skull. The bones fit together like a puzzle, and the areas where the bones meet one another are called the sutures, which are the fibrous joints. The bones and the sutures serve as a protective shield for the brain.

As the infant's brain grows rapidly during early infancy, the open sutures allow the skull to expand and to develop into a normal shape. However, if one or more of the sutures closes prematurely, either before birth or during the first few months of life, the skull compensates by expanding in the direction of the remaining open sutures, resulting in an abnormal shape. Children with craniosynostosis may also have increased pressure on the brain, resulting in developmental delays, and vision problems as a result of an imbalance in their ocular muscles. Craniosynostosis occurs in one out of 2,000 live births and affects males twice as often as females.

There are several types of craniosynostosis. The sagittal suture, the most common single suture involved in craniosynostosis, runs from a spot at the front of the head

to the back of the skull. In sagittal synostosis, the sagittal suture closes, resulting in the infant's head growing long and narrow, rather than expanding in width, in order to accommodate the growth of brain. There may or may not be bulging of both the front and back of the head.

The metopic suture runs from the nose up to the top of the skull, where it meets the sagittal suture. When the metopic suture closes, in metopic synotosis, the infant has a ridge down the forehead that can be seen or felt, and the forehead is narrow and triangular. The eyebrows may appear pinched on either side, and the eyes often seem to be close together. This head shape is referred to as trigonocephaly.

Early closure of one side of the coronal suture, which goes from ear to ear on the top of the head, is referred to as unilateral coronal synotosis (plagiocephaly). The forehead and orbital rim (eyebrow) have a flattened appearance on the affected side of the skull, resulting in a "winking" effect. In bicoronal synotosis, both sides of the coronal suture are fused, and the child may have a flat, recessed forehead. In addition, the head is short and wide, and there may be bulging of the eyes and bulging of the skull around the ears. This type of synotosis is most often found in children with Crouzon's and Apert's syndromes.

Lambdoid synotosis, the most rare form, resulting in bulging over the suture, and the ear on the affected side is pulled up and backwards over the suture, resulting in a flattening of the backside of the skull.

Multiple suture synotosis involves the fusing of all of the skull sutures. This condition requires emergency intervention.

The psychological effects of a noticeably misshapen forehead and face can be devastating to a child, resulting in low self-esteem and behavioral problems. Therefore it is important to correct cosmetic deformities of the skull and face.

Causes and symptoms

Most cases of craniosynostosis have no known causes. Some cases may be attributed to intrauterine restraint or early engagement of the head. Craniosynostosis is also associated with some known genetic chromosomal defects, including Apert, Crouzon, Pfieffer, and Saethre-Chotzen Syndromes.

Most children with craniosynostosis do not have any symptoms, except that the head shape is abnormal, and the face may be malformed. Rarely, the affected child may suffer symptoms such as increased pressure in the head, headaches, decreased appetite, vomiting, or even developmental delays or mental retardation.

Diagnosis

An infant with a distorted, misshapen head at birth should be examined by a pediatric neurosurgeon and a craniofacial surgeon to determine if the abnormality is due to abnormal fetal positions and neck tightness or due to craniosynotosis. The physical examination includes feeling the skull for suture ridges, spot spots, and checking the neck position, and taking measurements of the infant's face and head. Computerized tomography, which is a series of photographic images of the brain, is uses to diagnose early suture fusion and to develop surgical correction plans.

Treatment

Treatment of craniosynostosis is used to correct the deformities associated with craniosynotosis and is accomplished by restoring the normal shape and relationship of the forehead and orbital rims through craniofacial surgery. Surgery is less often needed to reduce intracranial pressure. In some cases helmet or band therapy is used after surgery to encourage further correction of the skull and face.

Ideally surgery to correct craniosynotosis should be carried out in an affected child who is less than three months old, when a less-invasive, microscopic procedure can be used that results in smaller incisions, less blood loss, and a shorter hospital stay than the traditional corrective surgery that is used on older children. Also the skull bones of an infant are easier to work with, and the covering of the brain, referred to as the dura, can make bone on its own. The growing brain continues to reshape the skull and face after surgery. However, surgery to correct craniosyntosis can be done at any age. Usually only one surgery is required to correct simple craniosynotosis, but some children may require minor surgery at 4-5 years of age to correct remaining minor abnormalities. When multiple sutures are involved, usually multiple surgeries are required.

The surgeons make an incision in the skull behind the hairline so that the scar will be covered by hair. The bone in the area of the defect is reshaped or replaced with bone from a different area of the skull.

Surgery for sagittal synostosis involves removing the suture and widening the skull by opening up the coronal and lambdoid sutures, which are found on both sides of the head. In some case bone grafts are used to keep the bones apart.

Surgery for unilateral coronal synotosis involves removing the fused suture, reshaping the forehead and brow, and bringing the forehead and brow forward to match the other side. The cheek is also brought forward

KEY TERMS

Synostosis—Union of two or more bones to form a single bone

to reposition the eye socket. For bicoronal synotosis, both sutures are removed, and the skull is narrowed and lengthened. Both cheekbones are brought forward to reposition the eye socket.

Metopic synotosis is corrected by releasing the metopic suture and expanding and rounding out the upper face, forehead, and skull. Surgery for lambdoid synotosis entails reconstruction of the back portions of the skull.

When all of the sutures are fused, the child must be operated on as soon as possible, with all of the sutures released and repositioned to allow for normal brain growth and to relieve the pressure on the eyes and brain.

Alternative treatment

Conventional surgical treatments should be relied upon for the treatment of craniosynotosis.

Prognosis

The prognosis for craniosynostosis is dependent on whether single or multiple cranial sutures are involved and whether other abnormalities are present. The prognosis is better when there is only single suture involvement and no abnormalities. Surgery is usually successful, and children can lead normal lives with no residual effects from craniosynostosis.

Prevention

Since the causes of craniosynostosis have not been identified, it is unknown as to what measures could be taken that would prevent the condition.

Resources

BOOKS

Parker, James M. and Parker, Philip M., editors. *The Official Parent's Sourcebook on Craniosynostosis*.San Diego, CA: Icon Health Publications, 2003.

PERIODICALS

ORGANIZATIONS

Children's Craniofacial Association, 13140 Coit Road, Suite 307, Dallas, TX 75240. Telephone: (800) 535-3643; Fax: (214) 570-3643. Web site: www.ccakids.com

OTHER

Craniosynostosis And Positional Plagiocephaly Support, Inc.6905 Xandu Court, Fredericksburg, VA 22407. Telephone: Website: http://www.cappskids.org

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Craniotomy

Definition

A craniotomy is the surgical removal of part of the skull to expose the brain.

Purpose

A craniotomy is the most commonly performed surgery to remove a brain tumor. It may also be done to remove a blood clot and control hemorrhage, to inspect the brain, to perform a **biopsy**, or to relieve pressure inside the skull.

Precautions

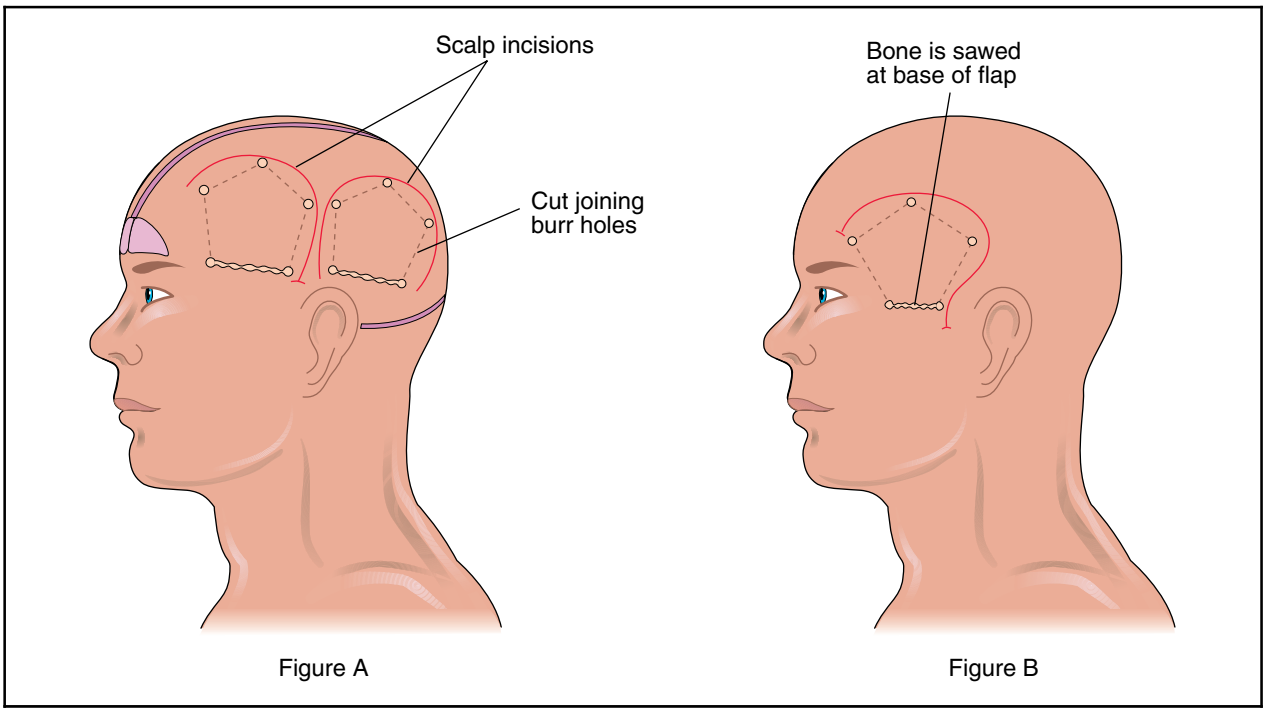
The outcome of surgery will depend on the type and location of the tumor. **Radiation therapy** or **chemotherapy** are sometimes given before surgery to shrink the tumor.

Description

There are two basic ways to open the skull. A curving incision may be made from behind the hairline, in front of the ear, to arch above the eye, or at the nape of the neck around the occipital lobe. The surgeon marks with a felt tip pen a large square flap on the scalp that covers the surgical area. Following this mark, the surgeon makes an incision into the skin as far as the thin membrane covering the skull bone. Because the scalp is well supplied with blood, the surgeon will have to seal many small arteries. The surgeon then folds back a skin flap to expose the bone.

Using a high speed hand drill or an automatic craniotome, the surgeon makes a circle of holes in the skull and pushes a soft metal guide under the bone from one hole to the next. A fine wire saw is then moved along the guide channel under the bone between adjacent holes. The surgeon saws through the bone until the bone flap can be removed to expose the brain.

After the surgery for the underlying cause is completed, the piece of skull is replaced and secured with pieces of fine, soft wire. Finally, the surgeon sutures the membrane, muscle, and skin of the scalp.



A craniotomy is the most commonly performed brain surgery for brain tumor removal. There are two basic ways to open the skull: a curving incision from behind the hairline in front of the ear and at the nape of the neck (figure A). To reach the brain, the surgeon uses a hand drill to make holes in the skull, pushing a soft metal guide under the bone. The bone is sawed through until the bone flap can be removed to expose the brain (figure B). *(Illustration by Electronic Illustrators Group.)*

Recent advances in computer-assisted technology have enhanced this operation. Image-guided craniotomy uses information from magnetic resonance imagining scans (MRIs) or **computed tomography** (CT) scans to produce three-dimensional images of the brain for the surgeon before the operation is begun. This makes it possible for the surgeon to remove less skin and bone, to tell exactly where the tumor stops and the healthy brain begins, and to remove tumors that were previously too deep for surgery.

Preparation

Before the operation, the patient undergoes diagnostic procedures such as CT and MRI scans to determine the underlying problem that requires the craniotomy and to get a better look at the brain's structure. Cerebral **angiography** is a diagnostic procedure that may be used to study the blood supply to the tumor, aneurysm, or other brain lesion.

Before the surgery, patients are given drugs to ease anxiety, and other medications to reduce the risk of swelling, seizures, and infection after the operation. Fluids may be restricted, and a diuretic (water pill) may be given before and during surgery if the patient has a tendency to retain water. A urinary catheter is inserted before the patient goes to the operating room. The scalp is shaved in the operating room immediately before surgery; this is done so that any small nicks in the skin won't have a chance to become infected before the operation.

Aftercare

Oxygen, painkillers, and drugs to control swelling and seizures are given after the operation. Codeine may be given to relieve potential headaches caused by the stretching or irritation of the nerves of the scalp. Some type of drainage from the head may be in place, depending on the reason for the surgery.

Patients are usually out of bed within a day and out of the hospital within a week. Headache and pain from the scalp wound can be controlled with medications. Some patients will receive radiation therapy or chemotherapy after surgery.

The bandage on the skull should be changed regularly. Sutures closing the scalp will be removed, but soft wires used to reattach the skull are permanent and require no further attention. The patient should avoid getting the scalp wet until all the sutures have been removed. A clean cap or scarf can be worn until the hair grows back.

KEY TERMS

Craniotome—A type of surgical drill used to operate on the skull. It has a self-controlled system that stops the drill when the bone is penetrated.

Computed tomography (CT or CAT) scan—Using x rays taken from many angles and computer modeling, CT scans help locate and size tumors and provide information on whether they can be surgically removed.

Magnetic resonance imaging (MRI)—MRI uses magnets and radio waves to create detailed cross-sectional pictures of the interior of the body.

Risks

Accessing the area of the brain that needs repair may damage other brain tissue. Therefore, the procedure carries with it risk of brain damage that could leave the patient with some loss of brain function. The surgeon performing the operation can give the patient an assessment of the risk of his or her particular procedure based on the location of the tumor.

Normal results

While every patient's experience is different depending on the reason for the surgery, age, and overall health, recovery from a successful surgery is usually rapid because of the good supply of blood to the area.

Abnormal results

Possible complications after craniotomy include:

- swelling of the brain
- excessive intracranial pressure
- infection
- seizures

See also Brain and central nervous system tumors; Computed tomography; Magnetic resonance imaging.

Resources

ORGANIZATIONS

American Cancer Society. 1599 Clifton Road NE, Atlanta, GA 30329. 800 (ACS)-2345). <http://www.cancer.org>.

Cancer Information Service, National Cancer Institute. Building 31, Room 10A19, 9000 Rockville Pike, Bethesda, MD 20892. (800) 4-CANCER. <http://www.nci.nih.gov/cancerinfo/index.html>.

Carol A. Turkington

Cryoablation

Definition

Cryoablation is the destruction of tissue by controlled freezing.

Purpose

Cryoablation, also called **cryotherapy**, is used primarily to treat male **prostate cancer**, although it can also be used in selective cases to treat abnormal uterine bleeding as an alternative to hysterectomy or to destroy certain localized liver tumors.

Cryotherapy came into use in 1966 with the development of thin probes that could be cooled to very low temperatures with liquid nitrogen. As of 2005, probes cooled with argon have been developed that can reach temperatures of -304°F (-187°C) causing quick and complete freezing of tissues.

Freezing tissue is thought to destroys cells in several ways. The formation of ice crystals inside the cells causes them to burst. Freezing also causes dehydration of certain cells and may destroy blood vessels supplying nutrients to the cells. In addition, freezing may activate an immune system response against the frozen tissue.

The prostate gland lies under the bladder and surrounds the urethra. Its main function is to produce seminal fluid that mixes with sperm prior to ejaculation. Prostate cancer is a leading cause of death in men.

Cryoablation of the prostate is not used as often as other therapies for prostate cancer. A survey of by the American Urological Association in 2001 found that fewer than 2% of urologists performed cryoablation, however the frequency with which these doctors performed the procedure was increasing. Medicare began paying for cryoablation procedures in 1999. Some private insurers will pay for the procedure, but only if the insured individual meets certain conditions with regard to his cancer status.

Advantages of cryoablation are that it is less invasive and less painful than surgery. The recovery period is short. The procedure can be performed again if it is not completely successful or the individual can receive additional therapies such as radiation or **chemotherapy**. The main disadvantages of cryoablation are that it does not destroy cancer cells that have spread beyond the prostate and that it has a high risk of causing impotence.

Precautions

Not all men with prostate cancer are good candidates for cryoablation. Those most likely to benefit from this procedure have low-risk tumors with their cancer

KEY TERMS

Androgens—Male hormones, most commonly testosterone.

Hysterectomy—Surgical removal of the uterus.

Prostate-specific antigen (PSA)—A type of protein made only by the prostate gland. High levels of PSA are a good indication of prostate cancer. Levels can be determined by a simple blood test.

Transrectal ultrasound—A procedure in which a device inserted into the rectum uses the echoes of sound waves to create an image of an organ or gland.

Urethra—The tube which drains urine from the bladder.

QUESTIONS TO ASK YOUR DOCTOR

- What stage is my cancer?
- Is my cancer confined to the prostate gland?
- Why do you recommend cryoablation over other available therapies?
- What experience do you have in performing prostate cryoablation? How many of these procedures do you perform each year?
- Will my insurance cover the cost of this procedure?

limited to the prostate gland. A second group of men who may benefit from this procedure are those whose cancer has not responded to **radiation therapy**, chemotherapy, and androgen withdrawal therapy. Men with very large prostates, those with urinary obstruction, and those who have had certain types of rectal surgery are not good candidates for this procedure.

Description

Cryoablation of the prostate is a minimally invasive procedure that is performed under general or regional anesthesia in a hospital or surgical clinic. An ultrasound device is inserted into the rectum to produce an image of the prostate and guide the placement of probes used to freeze the tissue. This procedure is called a transrectal ultrasound (TRUS). A catheter is inserted into the urethra and filled with warm saline (salt water) in order to avoid freezing the urethra.

Freezing of the prostate takes place one section at a time, with temperatures reaching -40°F (-40°C). The tissue is then allowed to thaw and a second cycle of freezing and thawing is performed after which the probes are removed. Patients may be kept overnight for observation after the procedure or discharged the same day.

Preparation

Prior to cryoablation, tests will be done to determine the size and shape of the prostate and the extent to which the cancer may have spread. Men with large prostates may be put on androgen deprivation therapy to shrink their prostate in order to make freezing more effective. The day before cryoablation is scheduled, the man will cleanse his bowel by drinking magnesium citrate. On the morning of the procedure, he will be administered an enema.

Aftercare

A catheter remains in the urethra for two to three weeks following the procedure. Because of swelling in of the urethra, the ability to urinate normally does not return for about two weeks. The individual may also be given **antibiotics** for 10–14 days after the procedure. A prostate-specific antigen (PSA) blood test and a prostate **biopsy** may be done three to six months following the procedure. If treatment is unsuccessful, individuals may receive chemotherapy, radiation therapy, or surgery.

Risks

Although technical advances have improved this procedure, significant risks still exist, because freezing is not always limited to cancerous tissue. This procedure results in a high rate (as much as 95%) of erectile dysfunction, although a few men (about 5%) regain function within a year and a half. Another significant risk is the development of a urinary-rectal fistula. This is an abnormal connection between the bladder and the rectum that can result in persistent urinary tract infections as feces leaks into the bladder. Other less common risks include an ongoing inability to empty the bladder, (although this is normal for a few weeks after the procedure), loss of bladder control, pelvic and rectal pain, and permanent numbness of the penis.

Normal results

Individuals with low- and moderate-risk tumors that have not spread beyond the prostate gland have a good

likelihood (60%ndash;75%) maintaining low PSA levels for five or more years, indicating that they are cancer free. For those with high-risk tumors, the success rate falls to about 40%.

Abnormal results

Failure of this therapy is indicated by rising PSA levels, presence of prostate cancer in post-treatment biopsy, or spread of cancer to other parts of the body.

Resources

ORGANIZATIONS

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Cryotherapy

Definition

Cryotherapy is a technique that uses an extremely cold liquid or instruments to freeze and destroy abnormal or cancerous skin cells that require removal. The prefix *cryo-* comes from the Greek word for frost. The technique has been in use since the turn of the century, but modern techniques have made it widely available to dermatologists and primary care doctors. Recent advances have also led to more frequent use of cryotherapy in treating internal cancer. The technique is also called cryosurgery.

Purpose

Cryotherapy can be employed to destroy a variety of such benign skin growths as warts, precancerous lesions (such as actinic keratoses), Bowen's disease, and such malignant lesions as basal cell and squamous cell carcinomas. It has also found new use in treating internal cancers, such as cancers of the prostate gland and the breast. The goal of cryotherapy is to freeze and destroy targeted skin growths or cancers while preserving the surrounding tissue from injury. For this reason cryosurgery appears to be useful in performing lumpectomies for smaller breast cancers.

Internal cancers that are being treated with cryosurgery as of 2003 include cancers of the kidney and liver as well as of the prostate gland.

Precautions

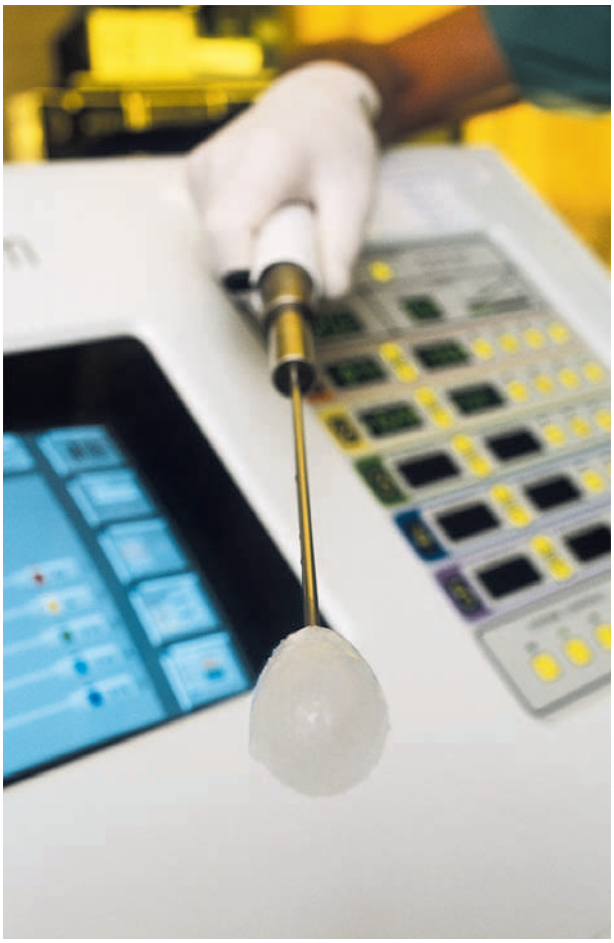
Cryotherapy is not recommended for certain areas of the body because of the danger of destruction of normal tissue or unacceptable scarring. These areas include: skin that overlies nerves, the corners of the eyes, the fold of skin between the nose and lip, the skin surrounding the nostrils, and the border between the lips and the rest of the face. Lesions that are suspected or known to be malignant **melanoma**, an aggressive form of skin cancer, should not be treated with cryotherapy, but should instead be removed surgically. Similarly, basal cell or squamous cell skin cancers that have reappeared at the site of a previously treated tumor should also be removed surgically.

If it remains unclear whether a growth is benign or malignant, a sample of tissue should be removed for analysis (**biopsy**) by a pathologist before any attempts to destroy the lesion with cryotherapy. Care should be taken in people with diabetes or certain circulation problems when cryotherapy is considered for growths located on their lower legs, ankles, and feet. In these patients, healing can be poor and the risk of infection can be high.

Description

There are three main techniques used to perform cryotherapy. In the simplest technique, usually reserved for warts and other benign skin growths, the physician will dip a cotton swab or other applicator into a cup containing a "cryogen," such as liquid nitrogen, and apply it directly to the skin growth to freeze it. At a temperature of −320 deg;F (−196°C), liquid nitrogen is the coldest cryogen available. The goal is to freeze the skin growth as quickly as possible, and then let it thaw slowly to cause maximum destruction of the skin cells. A second application may be necessary depending on the size of the growth.

In another cryotherapy technique, a device is used to direct a small spray of liquid nitrogen or other cryogen directly onto the skin growth. Freezing may last from 20–30 seconds, depending on the size of the lesion. A second freeze-thaw cycle may be required. In a third option, liquid nitrogen or another cryogen is circulated through a probe to cool it to low temperatures. The probe



Metal cryoprobe used to treat prostate cancer. *(Copyright Hank Morgan, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

is then brought into direct contact with the lesion, either on the skin or in the case of internal cancers, inside the patient. The freeze time can take two to three times longer than with the spray technique.

Preparation

Extensive preparation prior to cryotherapy is not required for external lesions. The area to be treated should be clean and dry, but sterile preparation is not necessary. Patients should know that they will experience some pain at the time of the freezing, but local anesthesia is usually not required. The physician may want to reduce the size of certain growths, such as warts, prior to the cryotherapy procedure, and may have patients apply salicylic acid preparations to the growth over several weeks. Sometimes, the physician will pare away some of the tissue using a device called a curette or a scalpel.

Preparation for treating cancers inside the body, such as **prostate cancer**, is slightly more complicated. The areas that are to be cooled are precisely mapped using ultrasound imaging or a specialized x-ray machine known as a computed axial tomography (CAT) scan. Temperature sensors are then placed inside and around the tumor to monitor the temperature. Lastly, cooling probes are then placed in and around the tumor.

Risks

Cryotherapy poses little risk and can be well tolerated by elderly and other patients who are not good candidates for other surgical procedures. As with other surgical procedures, there is some risk of scarring, infection, and damage to underlying skin and tissue. These risks are generally minimal in the hands of experienced users of cryotherapy.

Normal results

Some redness, swelling, blistering, and oozing of fluid are all common results of cryotherapy. Healing time can vary by the site treated and the cryotherapy technique used. When cryogen is applied directly to the growth, healing may occur in three weeks. Growths treated on the head and neck with the spray technique may take four to six weeks to heal; growths treated on other areas of the body may take considerably longer. Cryotherapy boasts high success rates in permanently removing skin growths; even for malignant lesions such as squamous cell and basal cell cancers, studies have shown a cure rate of up to 98%. For certain types of growths, such as some forms of warts, repeat treatments over several weeks are necessary to prevent the growth's return.

In the case of internal tumors, such as cancers of the prostate, cryotherapy has been shown to be at least as effective as other means, such as **radiation therapy**, with fewer side effects and faster recovery time. In addition, cryosurgery appears to have less severe effects on the patients' quality of life than other forms of treatment for prostate cancer.

Abnormal results

Although cryotherapy is a relatively low-risk procedure, some side effects may occur as a result of the treatment. They include:

- Infection. Though uncommon, infection is more likely on the lower legs where healing can take several months.
- Pigmentary changes. Both hypopigmentation (lightening of the skin) and hyperpigmentation (darkening of the skin) are possible after cryotherapy. Both generally last a few months, but can be longer lasting.

KEY TERMS

Actinic keratosis—A crusty, scaly precancerous skin lesion caused by damage from the sun. Frequently treated with cryotherapy.

Basal cell cancer—The most common form of skin cancer; it usually appears as one or several nodules having a central depression. It rarely spreads (metastasizes) but is locally invasive.

Cryogen—A substance with a very low boiling point, such as liquid nitrogen, used in cryotherapy treatment.

Melanoma—The most dangerous form of skin cancer. It should not be treated with cryotherapy but should be removed surgically instead.

Squamous cell cancer—A form of skin cancer that usually originates in sun-damaged areas or preexisting lesions; at first local and superficial, it may later spread to other areas of the body.

- Nerve damage. Though rare, damage to nerves is possible. Reports suggest this will disappear within several months.

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American Academy of Dermatology. 930 N. Meacham Road, P.O. Box 4014, Schaumburg, IL 60168-4014. (847)330-0230. <http://www.aad.org>.

OTHER

National Cancer Institute. <http://cis.nci.nih.gov>.

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CT-guided biopsy

Definition

A CT-guided **biopsy** is a procedure by which the physician uses a very thin needle and a syringe to withdraw a tissue or fluid specimen from an organ or suspected tumor mass. The needle is guided while being viewed by the physician on a **computed tomography** (CT) scan.

Purpose

A definite diagnosis of cancer is almost always based on the histological examination of cell or tissue samples. The procedure used to obtain a specimen for this testing is called a biopsy. Biopsies can be performed by surgical removal of the specimen if the suspicious area is located near the surface of the body or during surgery. If, however, the suspected tumor is located deep inside the body and cannot be seen or felt by the physician, he may decide to perform a CT-guided biopsy. The main advantage of a CT-guided biopsy is that it does not require an incision, but the disadvantage is that in some cases, the needle may not be able to remove enough tissue for analysis.

Precautions

CT-guided biopsy can be performed on almost all organs of the body, for example on the lungs, liver, kidneys, adrenal glands, pancreas, and pelvis. The procedure is not indicated for the spleen because there is a high risk of severe post-biopsy hemorrhage. CT-guided

KEY TERMS

Anesthesia—Loss of normal sensation or feeling. Insensitivity to pain.

Autopsy—Postmortem surgical procedure performed to examine body tissues and determine the cause of death.

Hemorrhage—Escape of blood from blood vessels; bleeding.

Histology—The study of tissue with a microscope.

Incision—Cutting through the skin.

Metastasis—The transfer of cancer from one organ to another one not directly connected to it.

Pelvis—Bassin-shaped body cavity containing and protecting the bladder, the rectum and the reproductive organs.

Pneumothorax—A collapse of the lung due to a sudden change of pressure within the chest cavity.

Sterile—Procedures carried out with instruments that have been sterilized, meaning that they are completely free from microorganisms (germs) that could cause infection.

QUESTIONS TO ASK THE DOCTOR

- Will the CT-guided biopsy procedure be painful?
- How many times will I need to have one?
- What is the normal success rate in obtaining enough tissue to make a diagnosis?
- What kind of complications may I experience at the biopsy site?
- When will I know the results?

biopsy is not indicated for patients with bleeding disorders such as hemophilia, or who are at risk for bleeding as a result of cancer treatments (chemo-radiation) or the cancer itself, as when a patient develops **thrombocytopenia**.

Description

The development of CT technology provided a powerful means to visualize the inner features of the human body which previously could only be seen during surgery or autopsy. Before CT, if a patient had a tumor located in the chest, abdomen, or pelvis, biopsies could only be performed with a surgical procedure. If the patient needed surgery so as to treat the tumor, then biopsy specimens were also collected at the same time for analysis. However, there was no way to obtain samples from patients whose tumors could not be treated with surgery, such as patients with metastatic cancer or with general conditions not allowing surgery. CT-guided needle biopsy has become a welcome alternative to surgical exploration and biopsy.

Preparation

The technique will vary depending on the site of specimen collection and the patient's general condition. In most procedures, the patient lies on the CT table on his back, or on either side, depending on where the needle is to be inserted. Some patients may require intravenous injection of pain killers. A CT scan is first performed, to locate the best site for needle insertion. The skin is then disinfected and anesthetized with its underlying tissue. The needle is inserted through the skin into the body. Another CT scan is perfomed to confirm that the tip of the needle lies at the desired location. When the tip of the needle is seen to be in the proper position, the biopsy specimen is withdrawn through the needle.

Aftercare

After the procedure, the patient is monitored in the hospital or clinic department or in an observation unit for a few hours, and then sent home.

Risks

CT-guided biopsy is a fairly safe procedure. The risks are certainly less than the risks involved with the alternative method, surgical biopsy. In any case, recovering from CT-guided biopsy takes considerably less time than it would if the biopsy were surgically performed.

The risks associated with CT-guided biopsy depend on the site where the biopsy specimen is collected. They include:

- Bleeding: Most patients have had their blood evaluated before the procedure. Although rare, bleeding can occur and may require surgery to control.
- Infection: An infection is possible whenever an object, —such as the needle used in CT-guided biopsy—, pierces the skin, —even if sterile procedures are always followed during the procedure. This is a very rare complication.
- Pneumothorax: Partial or total collapse of a lung is a reported complication in approximately 25% of lung biopsies. It is also a risk during CT-guided biopsies of the liver and adrenal glands.

Normal results

A preliminary evaluation of the CT-guided biopsy specimen is often performed by the physician. If enough tissue has been obtained for the required tests, the procedure is terminated and the specimen is sent to the histology lab for analysis.

Abnormal results

If the CT-guided biopsy has not been successful, it may be repeated or another biopsy procedure may be selected. Abnormal results indicate that a malignancy or other abnormality is present.

See also Biopsy; Imaging studies.

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Monique Laberge, Ph.D.

CT scan *see* **Computed tomography**

CUP *see* **Carcinoma of unknown primary**

Cushing's syndrome

Definition

Cushing's syndrome is a relatively rare endocrine (hormonal) disorder resulting from excessive exposure to the hormone cortisol. The disorder, which leads to a variety of symptoms and physical abnormalities, is most commonly caused by taking medications containing the hormone over a long period of time. A more rare form of the disorder occurs when the body itself produces an excessive amount of cortisol.

Description

The adrenals are two glands, each of which is perched on the upper part of the two kidneys. The outer part of the gland is known as the cortex; the inner part is known as the medulla. Each of these parts of the adrenal gland is responsible for producing different types of hormones. Regulation of hormone production and release from the adrenal cortex involves the pituitary gland, a small gland located at the base of the brain. After the hypothalamus (the part of the brain containing secretions important to metabolic activities) sends "releasing hormones" to the pituitary gland, the pituitary secretes a hormone called adrenocorticotropic hormone (ACTH). The ACTH then travels through the bloodstream to the adrenal cortex, where it encourages the production and release of cortisol (sometimes called the "stress" hormone) and other adrenocortical hormones.

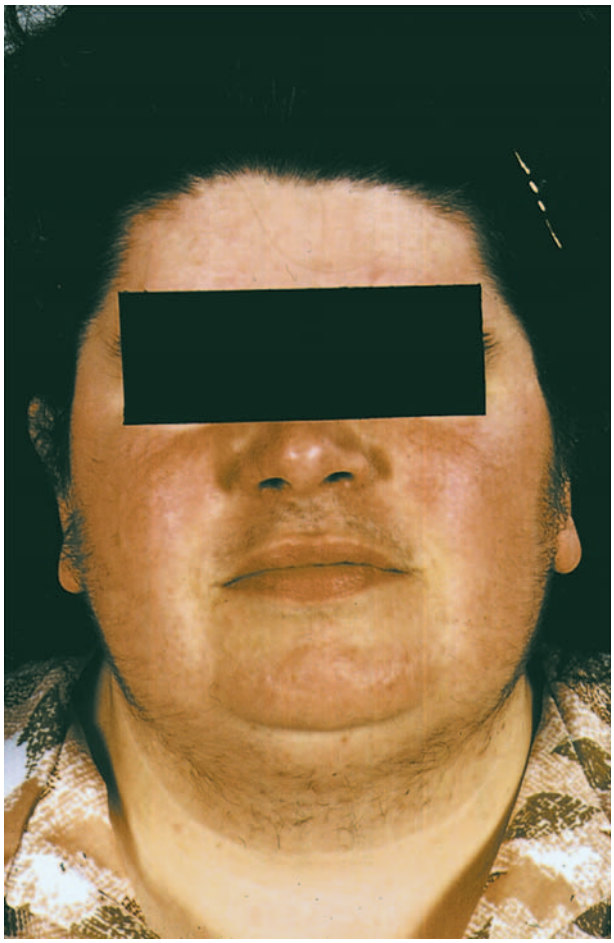
Cortisol, a very potent glucocorticoid—a group of adrenocortical hormones that protects the body from stress and affect protein and carbohydrate metabolism—is involved in regulating the functioning of nearly every type of organ and tissue in the body, and is considered to be one of the few hormones absolutely necessary for life. Cortisol is involved in:

- complex processing and utilization of many nutrients, including sugars (carbohydrates), fats, and proteins
- normal functioning of the circulatory system and the heart
- functioning of muscles
- normal kidney function
- production of blood cells
- normal processes involved in maintaining the skeletal system
- proper functioning of the brain and nerves
- normal responses of the immune system

Cushing's syndrome, also called hypercortisolism, has an adverse effect on all of the processes described above. The syndrome occurs in approximately 10 to 15 out of every one million people per year, usually striking adults between the ages of 20 and 50.

Causes and symptoms

The most common cause of Cushing's syndrome is the long-term use of glucocorticoid hormones in medications. Medications such as prednisone are used in a number of inflammatory conditions. Such conditions include rheumatoid arthritis, asthma, vasculitis, lupus, and a variety of other autoimmune disorders in which the body's immune cells accidentally attack some part of the body itself. In these disorders, the glucocorticoids are used to dampen the **immune response**, thereby decreasing damage to the body.



Woman exhibiting symptoms of Cushing's syndrome. *(Copyright John Radcliff Hospital/Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Cushing's syndrome can also be caused by three different categories of disease:

- a pituitary tumor producing abnormally large quantities of ACTH
- the abnormal production of ACTH by some source other than the pituitary
- a tumor within the adrenal gland overproducing cortisol

Although it is rare, about two-thirds of endogenous (occurring within the body rather than from a source outside the body, like a medication) Cushing's syndrome is a result of Cushing's disease. The term "Cushing's disease" refers to Cushing's syndrome, which is caused by excessive secretion of ACTH by a pituitary tumor, usually an **adenoma** (noncancerous tumor). The pituitary tumor causes increased growth of the adrenal cortex (hyperplasia) and increased cortisol production. Cushing's disease affects women more often than men.

Tumors in locations other than the pituitary can also produce ACTH. This is called ectopic ACTH syndrome ("ectopic" refers to something existing out of its normal place). Tumors in the lung account for more than half of all cases of ectopic ACTH syndrome. Other types of tumors which may produce ACTH include tumors of the thymus, the pancreas, the thyroid, and the adrenal gland. In each case, the secreting part of the tumor may be in the primary tumor, part of the primary tumor, or may be a small, difficult-to-find, metastatic lesion(s). Nearly all adrenal gland tumors are benign (noncancerous), although in rare instances a tumor may actually be cancerous.

Symptoms of cortisol excess (resulting from medication or from the body's excess production of the hormone) include:

- weight gain
- an abnormal accumulation of fatty pads in the face (creating the distinctive "moon face" of Cushing's syndrome); in the trunk (termed "truncal obesity"); and over the upper back and the back of the neck (giving the individual what has been called a "buffalo hump")
- purple and pink stretch marks across the abdomen and flanks
- high blood pressure
- weak, thinning bones (osteoporosis)
- weak muscles
- low energy
- thin, fragile skin, with a tendency toward both bruising and slow healing
- abnormalities in the processing of sugars (glucose), with occasional development of actual diabetes
- kidney stones
- increased risk of infections
- emotional disturbances, including mood swings, **depression**, irritability, confusion, or even a complete break with reality (psychosis)
- irregular menstrual periods in women
- decreased sex drive in men and difficulty maintaining an erection
- abormal hair growth in women (in a male pattern, such as in the beard and mustache area), as well as loss of hair from the head (receding hair line).

Diagnosis

Diagnosing Cushing's syndrome can be complex. Diagnosis must not only identify the cortisol excess but also locate its source. Many of the symptoms listed above can be attributed to numerous other diseases.

Although a number of these symptoms seen together would certainly suggest Cushing's syndrome, the symptoms are still not specific to Cushing's syndrome. Following a review of the patient's medical history, physical examination, and routine blood tests, a series of more sophisticated tests is available to achieve a diagnosis.

24-hour free cortisol test

This is the most specific diagnostic test for identifying Cushing's syndrome. It involves measuring the amount of cortisol present in the urine over a 24-hour period. When excess cortisol is present in the bloodstream, it is processed by the kidneys and removed as waste in the urine. This 24-hour free cortisol test requires that an individual collect exactly 24-hours' worth of urine in a single container. The urine is then analyzed in a laboratory to determine the quantity of cortisol present. This technique can also be paired with the administration of **dexamethasone**, which in a normal individual would cause urine cortisol to be very low. Once a diagnosis has been made using the 24-hour free cortisol test, other tests are used to find the exact location of the abnormality causing excess cortisol production.

Dexamethasone suppression test

This test is useful in distinguishing individuals with excess ACTH production due to a pituitary adenoma from those with ectopic ACTH-producing tumors. Patients are given dexamethasone (a synthetic glucocorticoid) orally every six hours for four days. Low doses of dexamethasone are given during the first two days; for the last two days, higher doses are administered. Before dexamethasone is administered, as well as on each day of the test, 24-hour urine collections are obtained.

Because cortisol and other glucocorticoids signal the pituitary to decrease ACTH, the normal response after taking dexamethasone is a drop in blood and urine cortisol levels. Thus, the cortisol response to dexamethasone differs depending on whether the cause of Cushing's syndrome is a pituitary adenoma or an ectopic ACTH-producing tumor.

However, the dexamethasone suppression test may produce false-positive results in patients with conditions such as depression, alcohol abuse, high estrogen levels, acute illness, and stress. On the other hand, drugs such as **phenytoin** and phenobarbital may produce false-negative results. Thus, patients are usually advised to stop taking these drugs at least one week prior to the test.

Corticotropin-releasing hormone (CRH) stimulation test

The CRH stimulation test is given to help distinguish between patients with pituitary adenomas and those with either ectopic ACTH syndrome or cortisol-secreting **adrenal tumors**. In this test, patients are given an injection of CRH, the corticotropin-releasing hormone that causes the pituitary to secrete ACTH. In patients with pituitary adenomas, blood levels of ACTH and cortisol usually rise. However, in patients with ectopic ACTH syndrome, this rise is rarely seen. In patients with cortisol-secreting adrenal tumors, this rise almost never occurs.

Petrosal sinus sampling

Although this test is not always necessary, it may be used to distinguish between a pituitary adenoma and an ectopic source of ACTH. Petrosal sinus sampling involves drawing blood directly from veins that drain the pituitary. This test, which is usually performed with

KEY TERMS

Adenoma—A type of noncancerous (benign) tumor that often involves the overgrowth of certain cells of the type normally found within glands.

Adrenocorticotropic hormone (ACTH)—A pituitary hormone that stimulates the cortex of the adrenal glands to produce adrenal cortical hormones.

Cortisol—A hormone secreted by the cortex of the adrenal gland. Cortisol regulates the function of nearly every organ and tissue in the body.

Ectopic—In an abnormal position.

Endocrine—Pertaining to a gland that secretes directly into the bloodstream.

Gland—A collection of cells whose function is to release certain chemicals (hormones) that are important to the functioning of other, sometimes distantly located, organs or body systems.

Glucocorticoids—General class of adrenal cortical hormones that are mainly active in protecting against stress and in protein and carbohydrate metabolism.

Hormone—A chemical produced in one part of the body, which travels to another part of the body in order to exert its effect.

Hypothalamus—the part of the brain containing secretions important to metabolic activities.

Pituitary—A gland located at the base of the brain, the pituitary produces a number of hormones, including hormones which regulate growth and reproductive function.

local anesthesia and mild sedation, requires inserting tiny, flexible tubes (catheters) through a vein in the upper thigh or groin area. The catheters are then threaded up slowly until they reach veins in an area of the skull known as the petrosal sinuses. X rays are typically used to confirm the correct position of the catheters. Often CRH is also given during the test to increase the accuracy of results.

When blood tested from the petrosal sinuses reveals a higher ACTH level than blood drawn from a vein in the forearm, the likely diagnosis is a pituitary adenoma. When the two samples show similar levels of ACTH, the diagnosis indicates ectopic ACTH syndrome.

Radiologic imaging tests

Imaging tests such as **computed tomography** scans (CT) and **magnetic resonance imaging** (MRI) are only used to look at the pituitary and adrenal glands after a firm diagnosis has already been made. The presence of a pituitary or adrenal tumor does not necessarily guarantee that it is the source of increased ACTH production. Many healthy people with no symptoms or disease whatsoever have noncancerous tumors in the pituitary and adrenal glands. Thus, CT and MRI is often used to image the pituitary and adrenal glands in preparation for surgery.

Treatment

The choice of a specific treatment depends on the type of problem causing the cortisol excess. Pituitary and adrenal adenomas are usually removed surgically. Malignant adrenal tumors always require surgical removal.

Treatment of ectopic ACTH syndrome also involves removing all of the cancerous cells which are producing ACTH. This may be done through surgery, **chemotherapy** (using combinations of cancer-killing drugs), or **radiation therapy** (using x rays to kill cancer cells), depending on the type of cancer and how far it has spread. Radiation therapy may also be used on the pituitary (with or without surgery), for patients who cannot undergo surgery, or for patients whose surgery did not successfully decrease pituitary release of ACTH.

There are a number of drugs that are effective in decreasing adrenal production of cortisol. These medications include **mitotane**, ketoconazole, metyrapone, trilostane, **aminoglutethimide**, and mifepristone. These drugs are sometimes given prior to surgery in an effort to reverse the problems brought on by cortisol excess. However, the drugs may also need to be administered after surgery (sometimes along with radiation treatments) in patients who continue to have excess pituitary production of ACTH.

Because pituitary surgery can cause ACTH levels to drop too low, some patients require short-term treatment with a cortisol-like medication after surgery. Patients who need adrenal surgery may also require glucocorticoid replacement. If the entire adrenal gland has been removed, the patient must take oral glucocorticoids for the rest of his or her life.

Prognosis

Prognosis depends on the source of the problem. When pituitary adenomas are identified as the source of increased ACTH leading to cortisol excess, about 80% of patients are cured by surgery. When cortisol excess is due to some other form of cancer, the prognosis depends on the type of cancer and the extent of its spread.

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Rosalyn Carson-DeWitt, M.D.

Cutaneous T-cell lymphoma

Definition

Cutaneous T-cell lymphoma (CTCL) is a malignancy of the T helper (CD4+) cells of the immune system.

Description

CTCL is a cancer of the white blood cells that primarily affects the skin and only secondarily affects other sites. The disease usually develops slowly, advancing from itchy dark patches on the skin to mushroom shaped tumors, a condition known as **mycosis fungoides**. This disease involves the uncontrollable proliferation of T-lymphocytes known as T helper cells, so named because of their role in the **immune response**. T-helper cells are characterized by the presence of a protein receptor on their surface called CD4. Accordingly, T-helper cells are said to be CD4+.

The proliferation of T-helper cells results in the penetration, or infiltration, of these abnormal cells into the epidermal layer of the skin. The skin reacts with slightly scaling lesions that itch, although the sites of greatest infiltration do not necessarily correspond to the sites of the lesions. The lesions are most often located on the trunk, but can be present on any part of the body. In the most common course of the disease, the patchy lesions progress to palpable plaques that are deeper red and have more defined edges. As the disease worsens, skin tumors develop that are often mushroom-shaped, hence the name mycosis fungoides (the name was not meant to imply that a fungus is involved in the disease). Finally, the cancer progresses to extracutanous involvement, often in the lymph nodes or the viscera.

The progression of the disease is often not linear, although the probability of spread to the viscera (internal organs in the abdomen) is directly related to the amount of skin involvement. Visceral involvement is almost never seen with minimal skin involvement. About 8% of those with generalized plaques have extracutaneous spread, while 30% with tumors have viscera involved. Overall, visceral involvement occurs with only 15 to 20% of all patients diagnosed with the disease.

Some patients present with an overall redness of the skin, with or without overlying plaques or tumors. The skin can be atrophic (shrunken) or lichenified (having small, firm bumps, close together), with cold intolerance and intense **itching**. These patients have swollen lymph nodes and large numbers of abnormal cells circulating the blood. This particular manifestation of CTCL is known as Sézary syndrome.

Demographics

CTCL is a rare disease, with an annual incidence of about .29 cases per 100,000 persons in the United States. It is about half as common in Eastern Europe. However, this discrepancy may be attributed to a differing physician awareness of the disease rather than a true difference in occurrence. In the U.S., there are about 500 to 600 new cases a year and about 100 to 200 deaths. Usually seen in older adults, CTCL strikes twice as many men as women and the median age at diagnosis is 55 to 60 years.

Causes and symptoms

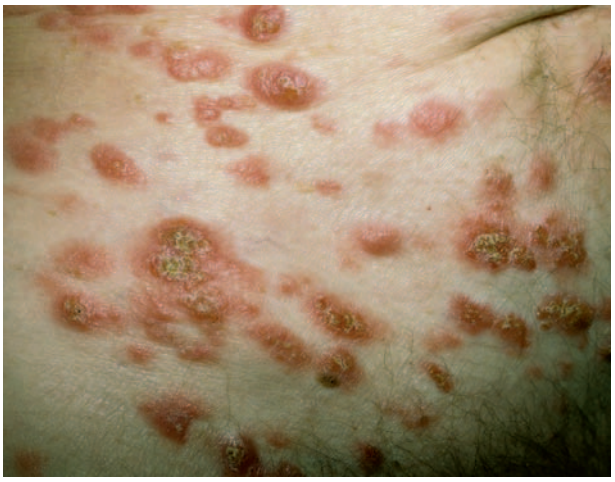
The cause of CTCL is unknown. Exposure to chemicals or pesticides has been suggested but the most recent study on the subject failed to show a connection between exposure and development of the disease. The ability to isolate various viruses from cell lines grown from cells of CTCL patients raises the question of a viral cause, but studies have been unable to confirm these suspicions.

The symptoms of CTCL are seen primarily in the skin, with itchy red patches or plaques and, usually over time, mushroom-shaped skin tumors. Any part of the skin can be involved and the extent and distribution of the rash or tumors vary greatly from patient to patient. The only universal symptom of the disease is the itch and this symptom is usually what brings the patient to the doctor for treatment. If the disease spreads outside of the skin, the symptoms include swelling of the lymph nodes, usually most severe in those draining the areas with skin involvement. Spread to the viscera is most often manifested as disorders of the lungs, upper digestive tract, central nervous system, or liver but virtually any organ can be shown to be involved at autopsy.

Diagnosis

Diagnosis of CTCL is often difficult in the early stages because of its slow progression and ability to mimic many other benign skin conditions. The early patches of CTCL resemble closely the rashes of eczema, psoriasis, and contact dermatitis. In a further complication, the early manifestations of the disease can respond favorably to the topical corticosteroid treatments prescribed for these skin disorders. This has the unfortunate result of the disease being missed and the patient remaining untreated for years. CTCL is most likely discovered when a physician maintains a suspicion about the disease, performs multiple skin biopsies, and provides close follow-up after the initial presentation.

Skin biopsies showing penetration of abnormal cells into the epidermal tissue are necessary to make a firm diagnosis of CTCL. Several molecular studies can also help support the diagnosis. The first looks at the cellular proteins seen on the surface of the abnormal cells. Many cases of CTCL show the retention of the CD4+ protein, but the loss of other proteins usually seen on the surface of



Itchy, crusted plaque on the skin of a patient with cutaneous T-cell lymphoma. *(Custom Medical Stock Photo. Reproduced by permission.)*

mature CD4+ cells, such as Leu-8 or Leu-9. The abnormal cells also show unusual rearrangements at the genetic level for the gene that encodes the T-cell receptors. These rearrangements can be identified using Southern blot analysis. The information from the molecular tests, combined with the presence of abnormal cells in the epidermis, strongly supports the CTCL diagnosis.

Treatment team

This disease is treated by a dermatologist, a medical oncologist, and, if **radiation therapy** is used, a radiation oncologist.

Clinical staging, treatments, and prognosis

The current staging of this disease was first presented at the International Consensus Conference on CTCL in 1997. This staging attempts to show the complex interaction between the various outward symptoms of the disease and prognosis. The system has seven clinical stages based on skin involvement (tumor = T), lymph node involvement (LN), and presence of visceral metastases (M).

The first stage, IA, is characterized by plaques covering less than 10 percent of the body (T1) and no visceral involvement (M0). Lymph node condition at this stage can be uninvolved, reactive to the skin disease, or dermatopathic (biopsies showing CTCL involvement) but not enlarged (LN0-2). The shorthand expression of this stage is therefore T1, LN0-2, M0. Prognosis is very good if the disease has only progressed this far, with an average survival of 20 or more years. Most deaths occurring to persons in this group are unrelated to CTCL.

The next stage, IB, differs from IA in that greater than 10 percent of the body is covered by plaques (T2, LN0-2, M0). Stage IIA occurs with any amount of plaques in addition to the ability to palpate the lymph node and the lymph uninvolved, reactive, or dermatopathic (T1-2, LN0-2, M0). Average survival for patients in stages IB and IIA is about 12 years.

Treatments applied to the skin are preferred for patients having these preliminary stages of the disease. These commonly include topical **chemotherapy** with **mechlorethamine** hydrochloride (nitrogen mustard) or phototherapy of psoralen plus ultraviolet A (PUVA). Topical chemotherapy involves application to the skin of nitrogen mustard, an alkylating agent, in a concentration of 10 to 20 mg/dL in an aqueous or ointment base. Treatment of affected skin is suggested at a minimum and application over the entire skin surface is often recommended. Care needs to be taken that coverage of involved skin is adequate, as patients who self-apply the drug often cannot reach all affected areas. The most common side effect is skin hypersensitivity to the drug. Nearly all patients respond favorably to this treatment, with a 32 to 61% complete response rate, based on amount of skin involvement. Unfortunately, only 10 to 15% of patients maintain a complete response rate after discontinuing the treatment.

Phototherapy involves treatment with an orally administered drug, 8-methyloxypsoralen, that renders the skin sensitive to long-wave ultraviolet light (UVA), followed by controlled exposure to the radiation. During the initial treatment period, which may last as long as 6 months, patients are treated two to three times weekly. This is reduced to about once monthly after initial clearing of the lesions. Redness of the skin and blistering are the most common side effects of the treatment and are much more common in patients presenting with overall skin redness, or erythroderma, so lower intensities of light are usually used in this case. About 50% of all patients experience complete clearance with this treatment. Some patients with very fair skin and limited skin involvement can successfully treat themselves at home with special lamps and no psoralen.

The next stage, IIB, involves one or more cutaneous tumors, in combination with absent or present palpable lymph nodes, lymph uninvolved, reactive, or dermatopathic, and no visceral involvement (T3, LN0-2, M0). Stage III is characterized by erythroderma, an abnormal redness over widespread areas of the skin (T4, LN0-2, M0). The disease in both of these stages involves intermediate risk to the patient.

For more extensive disease, radiation therapy is an effective treatment option. It is generally used after the

topical treatments have proven ineffective. Individual plaques or tumors can be treated using electrons, orthovoltage x rays, or megavoltage photons with exposure in the range of 15 to 25 Gy. Photon therapy has proven particularly useful once the lymph nodes are involved. Another possibility is total-skin electron beam therapy (TSEB), although the availability of this treatment method is limited. It involves irradiation of the entire body with energized electrons. Side effects of this treatment include loss of finger and toe nails, acute redness of the skin, and inability to sweat for about 6 to 12 months after therapy. Almost all patients respond favorably to radiation treatment and any reoccurrence is usually much less severe.

Combinations of different types of treatments is a very common approach to the management of CTCL. Topical nitrogen mustard or PUVA is often used after completion of radiation treatment to prolong the effects. The addition of genetically engineered interferon to PUVA therapy significantly increases the percentage of patients showing a complete response. Furthermore, although treatments using chemotherapy drugs alone, such as deoxycofomycin or etretinate, have been disappointing for CTCL, combining these drugs with interferon has shown promising results. Interferon has also been combined with retinoid treatments, although the mechanism of action of retinoids (Vitamin A analogues) against CTCL is unknown.

The final two stages of the disease are IVA and IVB. IVA presents as any amount of skin involvement, absent or present palpable lymph nodes, no visceral involvement, and lymph that contains large clusters of convoluted cells or obliterated nodes (T1-4, LN3-4). Patients in stage III and IVA have an average life expectancy of about five years. IVB differs in the addition of palpable lymph nodes and visceral involvement (T1-4, LN3-4, M1). At these stages the disease is high risk, with most deaths occurring by infection, due to the depleted immune system of the later stage patient. Once a patient has reached stage IVB, the average life expectancy is one year. All of the treatment methods described above are appropriate for the final two stages of the disease.

Alternative and complementary therapies

Itching of the skin is one of the most troublesome symptoms of CTCL. One alternative treatment for itchiness is the application of a brewed solution of chickweed that is applied to the skin using cloth compresses. Another suggested topical application is a mixture of vitamin E, vitamin A, unflavored yogurt, honey, and zinc oxide. Evening primrose oil applied topically may also reduce itch and promote healing.

KEY TERMS

Alkylating agent—A chemical that alters the composition of the genetic material of rapidly dividing cells, such as cancer cells, causing selective cell death; used as a topical chemotherapeutic agent to treat CTCL.

Erythroderma—An abnormal reddening of the entire skin surface.

Mycosis fungoides—A well-defined subset of CTCL in which mushroom shaped tumors form on the skin.

Retinoids—A group of natural and synthetic compounds that resemble vitamin A in their activity. Retinoids are used in the treatment of CTCL.

Sézary syndrome—A variant of CTCL that is characterized by circulating abnormal T cells and erythroderma.

T-helper cells—A cellular component of the immune system that plays a major role in ridding the body of bacteria and viruses, characterized by the presence of the CD4 protein on its surface; the type of cell that divides uncontrollable with CTCL.

Total-skin Electron Beam Therapy—A method of radiation therapy used to treat CTCL that involves bombarding the entire body surface with high energy electrons.

Coping with cancer treatment

Topical chemotherapy and radiation treatment of the skin require special care of the areas being exposed to the drug or emission. Use of mild soap and special sensitive formulas for moisturizer and other skin products is suggested. Tight clothing in the area should be avoided. It is important that the treated area is not exposed to the sun during the treatment course. In general, special care to not irritate the area that is being treated will help ease the treatment course.

Clinical trials

Recent **clinical trials** for CTCL have focused on testing molecular treatment approaches. Anti-T-cell **monoclonal antibodies**, that would theoretically target the abnormal T cells for destruction by the patient's own immune system, have been tried. Unfortunately, the responses to this treatment have been brief and limited by the development of an immune reaction against the antibodies themselves (which are made in mouse cells

QUESTIONS TO ASK THE DOCTOR

- What is the stage of the disease at this point and what is the prognosis?
- What are the treatment options and what side effects can be expected?
- Is total-skin electron beam therapy (TSEB) available and is this a treatment that should be considered?
- What are the chances of complete clearance of the disease?

and therefore seen as foreign by the patient's immune system). Studies continue using newly developed, more specific antibodies and radiolabeled antibodies (to target radiation therapy to the T-helper cells).

Genetically engineered fusion proteins that link diphtheria toxin (a protein that kills cells) with interleukin-2 (a protein that binds to T-helper cells through a receptor on its surface) have also been administered intravenously to CTCL patients. The toxin was taken into the abnormal cells and did kill them. Three out of five patients in a phase I trial achieved significant tumor response to this novel therapy.

As of 2003, other experimental treatments for CTCL include imiquimod, an immune response modifier available as a topical cream; denileukin-diftitox (Ontak), a drug given by injection; doxorubicin; and various combinations of these agents.

Additional new approaches to the treatment of CTCL include vaccine therapy and stem cell transplantation. A group of researchers in Japan is currently testing various peptides introduced through the skin as a possible form of immunization against CTCL, while German and American researchers are investigating the potential of stem cell transplantation in the treatment of CTCL. As of late 2003, bone marrow transplants from unrelated donors offer the best hope of a curative treatment for CTCL.

Prevention

Studies have been unable to link CTCL to any environmental or genetic factors, so prevention is not possible as of the early 2000s.

Special concerns

Because the initial diagnosis of CTCL can be difficult, any dermatitis-like or eczema-like rash that does not respond to treatment or recurs after running the full course of topical **corticosteroids** should be brought to the attention of a doctor. This is particularly important given the good prognosis with early diagnosis and treatment of CTCL but rapidly worsening prognosis with progression of the disease.

See also Non-Hodgkin's lymphoma.

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National Cancer Institute. Building 31 Room 10A31 31 Center Drive MSC 2580 Bethesda, MD 20892-2580. (800)4-CANCER. <http://cancernet.nci.nih.gov>.

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Rebecca J. Frey, PhD

Cyclooxygenase 2 inhibitors

Definition

Cyclooxygenase 2 inhibitors, also known as COX-2 inhibitors, are useful as pain and antiflammatory medications for cancer patients. COX-2 inhibitors are not better at stopping pain and inflammation than other non-steroidal anti-inflammatory drugs (NSAIDs), but are less likely to cause stomach ulcers and bleeding.

Purpose

Nonsteroidal anti-inflammatory drugs (NSAIDs) used to treat pain and inflammation are relatively effective in controlling these symptoms but can cause serious side effects. These side effects include stomach ulcers, kidney problems, and increased likelihood of bleeding. Aspirin is the most serious offender, although other pain medications in the NSAID class of medication present similar problems. COX-2 inhibitors were developed as a type of pain medication less likely to cause stomach and bleeding problems than existing NSAID pain medications.

COX-2 inhibitors may also have future applications in cancer therapy. Recent research suggests that COX-2 is involved in the growth of cancerous tumors; therefore, COX-2 inhibitors may prove to be helpful in preventing or slowing the growth of certain types of cancer. One group of researchers in Taiwan reported in 2003 that celecoxib inhibits the growth of cell lines derived from mouth cancers, while another group in Arizona found that COX-2 inhibitors may be effective in slowing the growth of malignant melanoma.

Description

Cyclooxygenase is a chemical important for the normal functioning of the human body. Cyclooxygenase helps the stomach and kidneys to function normally, the platelets in the blood to function normally, and the brain to regulate body temperature and feel pain. Scientists have discovered that there are two distinct types of cyclooxygenase (abbreviated COX). These two types of COX are known as COX-1 and COX-2. COX-1 is needed to maintain the normal body functions of platelet aggregation, the regulation of blood flow in the kidney and stomach, and the regulation of gastric acid secretion in the stomach.

COX-2 is produced only when the body's tissues have been injured. COX-2 mediates inflammation, helps the nerves feel pain, and helps the brain regulate **fever**. A medication that inhibits COX-2 can suppress inflammation, relieve pain, and reduce fever. Inhibition of COX-1, on the other hand, results in bleeding and kidney and stomach toxicity.

The problem with many older pain medications is that they affect both COX-1 and COX-2, even though they provid benefit only through how they affect COX-2. That is why their long-term use may be associated with such side effects as stomach ulcers, decreased kidney function, and a tendency for excessive bleeding. COX-2 inhibitors inhibit COX-2 while exerting less effect on COX-1.

At the end of 2003, three COX-2 inhibitors were available by prescription in the United States. Celecoxib (brand name Celebrex) was the first to be made available, followed by rofecoxib (brand name Vioxx) and valdecoxib (brand name Bextra), which was approved by the Food and Drug Administration (FDA) in late 2001. In addition, the pharmaceutical company Novartis had hoped to secure FDA approval in 2003 for a fourth COX-2 inhibitor named lumiracoxib, to be sold under the brand name Prexige. The FDA requested more data, however, and as of 2004 lumiracoxib has not yet been approved for use in the United States.

The FDA's reluctance to approve lumiracoxib may have been prophetic, insofar as the agency issued a public health advisory in late September 2004 regarding the safety of rofecoxib. The FDA was concerned about reports that Vioxx increased patients' risks of heart attack or stroke. The manufacturer voluntarily removed the drug from the market on September 30, 2004.

Recommended dosage

Celecoxib comes in 100 mg and 200 mg capsules that are taken orally either once or twice a day.

Valdecoxib is available in 10 and 20 mg tablets.

Precautions

Celecoxib should not be taken by patients with sulfonamide allergy. This medication should not be taken during the last few months of pregnancy.

Valdecoxib should not be taken during the last trimester of pregnancy. In addition, patients taking valdecoxib should tell their doctor if they are pregnant or might become pregnant during treatment with the drug.

Side effects

Celecoxib has few side effects. A small number of patients report stomach upset and even fewer report abdominal pain. Other effects reported rarely with celecoxib include kidney problems, fluid retention, and retention of water in the tissues. The occurrence of ulcers

KEY TERMS

Cyclooxygenase—A chemical important for the normal functioning of the human body. The body produces cyclooxygenase 1 (COX 1) and cyclooxygenase 2 (COX 2).

Cyclooxygenase 1 (COX 1) —The cyclooxygenase that helps the stomach, kidneys, and blood function well.

Cyclooxygenase 2 (COX 2)—The cyclooxygenase that helps mediate inflammation and that helps the brain feel pain and regulate fever.

in patients taking celecoxib is less frequent than for many other pain medications. However, the long-term safety of celecoxib has not been well-researched.

Valdecoxib has been reported to cause weight gain, skin rashes, nausea and abdominal pain, itching, yellowing of the skin, flu-like symptoms, or unusual bruising or bleeding in some patients.

Interactions

Celecoxib may affect the activities of **warfarin**, a medication that limits the ability of blood to clot. Celecoxib may also be involved in interactions with: furosemide, a diuretic; angiotensin-converting enzyme inhibitors (ACE inhibitors), medicines used for high blood pressure and some heart problems; lithium, a medication for bipolar disorder; and fluconazole, an antifungal medication. Celecoxib may be taken with any of the medicines mentioned above—however, the doctor should closely monitor these drug combinations. Because celecoxib is a relatively new medication, more remains to be learned about its potential to interact with other drugs.

Valdecoxib may interact with NSAIDs, aspirin, lithium, steroid medications, ACE inhibitors, blood thinners (anticoagulants), and diuretics. In general, patients should make sure that their doctor has a complete list of all medications that they take on a regular basis—including over-the-counter pain relievers—before taking any COX-2 inhibitor.

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Bob Kirsch
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Cyclophosphamide

Definition

Cyclophosphamide is an anticancer (antineoplastic) agent. It also acts as a suppressor of the immune system. It is available under the brand names Cytoxan and Neosar.

Purpose

Cyclophosphamide is approved by the Food and Drug Administration (FDA) to treat several forms of cancer. These include:

- breast cancer
- leukemia
- malignant lymphoma
- multiple myeloma
- ovarian cancer
- soft tissue sarcoma
- mycosis fungoides
- nephrotic syndrome
- neuroblastoma
- Wilms' tumor
- retinoblastoma

Cyclophosphamide has activity against a wide variety of other cancers and conditions not specifically approved by the FDA, and patients should be aware that it may be commonly prescribed for these other disease states:

- bone cancer
- cervical cancer
- endometrial cancer
- germ cell tumors
- gestational trophoblastic tumors
- histiocytosis X
- lung cancer
- prostate cancer
- testicular cancer
- Wilms' tumor

Description

Cyclophosphamide chemically interferes with the synthesis of the genetic material (DNA and RNA) of cancer cells by cross-linking DNA strands, preventing these cells from being able to reproduce and continue the growth of the cancer.

Recommended dosage

Cyclophosphamide may be taken either orally (in pill form) or as an injection into the vein. The dosage prescribed may vary widely depending on the patient, the cancer being treated, and whether or not other medications are also being taken.

A typical oral dosage for adults is 1 to 5 mg per kg of body weight per day for initial and maintenance dose, or 400 to 1000 milligrams per squared meter of body surface area for four to five days every three to four weeks. A typical dosage by injection is 40 to 50 mg per kg, divided in several smaller doses, for two to five days. The dose for patients receiving bone marrow transplant may be as high as 60 mg per kg per day for two days.

Precautions

Cyclophosphamide should be taken on an empty stomach. If stomach irritation occurs, it should be taken with small amounts of food or milk. Cyclophosphamide should always be taken with plenty of fluids.

Cyclophosphamide can cause an allergic reaction in some people. Patients with a prior allergic reaction to cyclophosphamide should not receive this drug.

Cyclophosphamide can cause serious birth defects if either the man or the woman is taking this drug at the time of conception or if the woman is taking this drug during pregnancy. Contraceptive measures should be taken by both men and women while on this drug. Sterility is a common side effect of cyclophosphamide. This sterility is dependent upon the dose, duration of therapy, and state of function of the ovary or testicle at the time of administration of the drug. The sterility may be irreversible in some patients.

Because cyclophosphamide is easily passed from mother to child through breast milk, breast feeding is not recommended while under treatment.

Cyclophosphamide suppresses the immune system and interferes with the normal functioning of certain organs and tissues, and its excretion from the body is dependent on a normal functioning kidney and liver. For these reasons, it is important that the prescribing physician is aware of any of the following pre-existing medical conditions:

- a current case of, or recent exposure to, chicken pox
- herpes zoster (shingles)
- all current infections
- kidney disease
- liver disease
- a prior removal of one, or both, adrenal gland(s)

Also, because cyclophosphamide is such a potent immunosuppressant, patients taking this drug must exercise extreme caution to avoid contracting any new infections.

Side effects

Inflammation and irritation of the bladder, causing blood in the urine, is a common and severe side effect of cyclophosphamide. However, this side effect can be prevented and controlled with the administration of vigorous hydration with intravenous fluids before, during, and after **chemotherapy**. Patients should urinate frequently (at least every 2 hours) to enhance removal of the drug from the body, drink 3 to 4 liters of fluids a day while taking the drug by mouth and for 2 to 3 days after discontinuation of the drug unless otherwise instructed by the physician. Patients who are taking cyclophosphamide orally should avoid taking the drug at night so that they can go to the bathroom frequently during the day. The bladder-protectant drug **mesna** is usually administered if the patient is receiving more than 2,000 mg per square meter of body surface area of the cyclophosphamide. Another common side effect of cyclophosphamide is increased susceptibility to infection due to decreased production of cells that fight infection. Increased risk of bleeding can occur due to decrease of platelets, which are involved with the clotting process. Decreased

KEY TERMS

Antineoplastic—A drug that prevents the growth of a neoplasm by interfering with the maturation or proliferation of the cells of the neoplasm.

Neoplasm—New abnormal growth of tissue.

production of red blood cells can cause **anemia** and patients may experience **fatigue**, and shortness of breath.

Nausea and vomiting can occur, usually at the higher doses. Taking the appropriate **antiemetics** prescribed by the physician can prevent this side effect. Temporary hair loss (alopecia) usually begins three to six weeks after the start of therapy, but hair will regrow (although it may be a different color and/or texture). Sterility can occur in both men and women, and some women may also experience stoppage of menstruation. **Diarrhea** and ulcers of the mouth are also possible side effects of cyclophosphamide treatment.

Less common side effects include:

- nasal stuffiness
- runny eyes
- runny nose
- sinus congestion
- dizziness
- darkening of skin or fingernails
- skin rash
- sneezing (if the drug is given too rapidly by injection into the vein
- facial flushing

Some patients may also develop a second cancer years later with cyclophosphamide therapy alone or in combination with other anti cancer drugs. Patients should discuss this side effect with their physicians and determine the risks versus the benefits of this drug for treatment of the immediate cancer.

A doctor should be consulted immediately if the patient experiences any of the following:

- painful or difficult urination
- increase in frequency or feeling of urgency to urinate
- blood in the urine
- shortness of breath
- signs of infection such as cough, sore throat, **fever** and chills
- pain in the lower back or sides
- unusual bleeding or bruising
- blood in the stool
- tiny red dots on the skin
- delayed healing of any wounds
- skin rash
- yellowing of the skin or eyes

Interactions

Cyclophosphamide should not be taken in combination with any prescription drug, over-the-counter drug, or herbal remedy without prior consultation with a physician.

Paul A. Johnson, Ed.M.

Cyclosporine

Definition

Cylosporine is an immunosuppressant drug used to prevent rejection of kidney, liver, and heart transplants, to prevent graft-versus-host disease in patients receiving allogeneic bone marrow transplants, and for severe autoimmune diseases that are resistant to **corticosteroids** and other therapy. Cyclosporine, also spelled as cyclosporin and ciclosporin, takes several brand names in the United States, including Neoral, Sandimmun, Sandimmune, and Sang Cya. It is also known in slight variant forms, such as cyclosporin A, CsA, and CyA. The Neoral and Sang Cya brand name products are interchangeable, but the Sandimmune brand name product can not be used interchangeably for those other two products.

Purpose

Cyclosporine is best known as a drug used to prevent the rejection of organ transplants and bone grafts.

Description

Discovered in 1972, cyclosporine was first isolated from a fungus. It suppresses (prevents the activity of) the cells in the lymphatic system, known as T cells, that would otherwise mount an **immune response**. This suppression makes cyclosporine useful in conjunction with organ transplants. (In a transplant, the patient receiving a donated organ can react to the organ as though it were a

foreign substance, rejecting it.) Cyclosporine is also used to treat severe rheumatoid arthritis, and is being used investigationally as a drug that may help to temper multi-drug resistance in cancer patients.

The drug is available in several forms, including an intravenous (I.V.) solution, an oral solution, and an oral capsule. Cyclosporine is broken down in the liver.

Recommended dosage

The dosage varies, depending on the reason for use and the patient, and the dosage is also often adjusted by the physician. The dosage is based on the patient's ideal body weight, and the oral dose is approximately three times higher than the intravenous dose. I.V. use is only reserved for patients who cannot take the oral dose, and it is recommended that patients who can be switched to the oral form be switched as soon as possible.

The usual initial oral dose is 14–18 mg/kg per day, beginning four–twelve hours before organ transplantation. After the transplantation, the dose is decreased, and then usually tapered to 3–10 mg/kg per day.

Precautions

Cyclosporine can cause infection and possibly **lymphoma**, and is toxic to the kidneys. The use of this drug along with other drugs that are toxic to the kidneys must be closely monitored. It should be ingested and swallowed in its capsule without breaking the capsule. The liquid solution should only be mixed in a glass container. Pregnant or nursing women should not take this drug, and patients taking this drug will be more susceptible to infection. Therefore, crowds of people should be avoided, and no live **vaccines** should be adminstered to the patient without consulting the patient's doctor. Patients should inform their doctor of any hypersensitivities or drug allergies they have before taking this drug. (Cyclosporine in both liquid and capsule form has some castor oil components in it, which could cause an allergic reaction for some.) Some allergic reactions to the I. V. solution may be severe. This drug has not been specifically studied for use with the elderly.

Side effects

More than 10% of patients taking this drug experience the following:

- high blood pressure
- unusual hair growth
- kidney toxicity
- tremors
- thickening of the gums

KEY TERMS

Intravenous line—A tube that is inserted directly into a vein to carry medicine directly to the bloodstream, bypassing the stomach and other digestive organs that might alter the medicine.

Lymphatic system—The system that collects and returns fluid in tissues to the blood vessels and produces defensive agents for fighting infection and invasion by foreign bodies.

Kilogram (kg)—Metric measure that equals 2.2 pounds.

Milligram (mg)—One-thousandth of a gram. A gram is the metric measure that equals about 0.035 ounces.

Other, less common side effects include: seizures, headache, acne, abdominal pain, **nausea and vomiting**, leg cramps, and some endocrine/metabolic conditions known as hypomagnesia, hypokalemia, hyperkalemia, and hyperlipidemia.

Interactions

Cyclosporine interacts with a long list of other drugs. A physician should be informed about each and every drug a person eligible for treatment with cyclosporine is taking. Drugs that may make cyclosporine less effective include: **carbamazepine**, phenobarbital, **phenytoin**, and others. Drugs that may increase cyclopsporine's toxicity include: acyclovir, amphotericin B, corticosteroids, erythromycin, certain **antibiotics**, and some antifungals including fluconazole, itraconazole, and ketaconazole. Cyclosporine should not be taken with grapefruit or related juices because the combination can make it more toxic. Vaccinations should not be given while a person is taking cyclosporine.

Diane M. Calabrese

Cystosarcoma phyllodes

Definition

Cystosarcoma phyllodes (CSP) is a rare type of breast tumor. It is categorized by the National Cancer Institute (NCI) as a tumor subtype that occurs within the

breast but is not considered a typical cancer. Its name comes from two Greek words that mean "fleshy tumor" and "leaflike," because its internal structure resembles a leaf when the tumor is cross-sectioned. The term phyllodes tumor is considered preferable to CSP as of the early 2000s because most of these tumors are benign. Phyllodes tumors are also known as giant fibroadenomas of the breast.

Description

Phyllodes tumors develop only in the breast; they are never found in other parts of the body. They are formed within the stroma (connective tissue) of the breast and contain glandular as well as stromal tissue. Phyllodes tumors can grow noticeably within a matter of weeks, causing the overlying skin to become semi-transparent or reddish and warm to the touch. They do not, however, usually involve the nipple or areola.

A phyllodes tumor can be moved freely within the breast when the doctor performs a manual examination. The tumor has a firm, smooth texture, can be easily distinguished from the surrounding tissue, and may grow to be quite large and bulky. The average size of phyllodes tumors is about 2 in (5 cm), although tumors as large as 11.8 in (30 cm) have been reported. These tumors do not cause pain when touched. For reasons that are not yet understood, phyllodes tumors are more likely to develop in the left breast than the right.

There is some disagreement among specialists regarding the number of phyllodes tumors that prove to be malignant. Although figures of 16–30 percent are commonly given, some doctors think that the actual incidence may be higher, as more cases of malignant tumors have been reported in the early 2000s.

Demographics

Phyllodes tumors account for less than 1 percent of all breast tumors. Almost all occur in women, although a few cases have been reported in men. Phyllodes tumors have been identified in women in all age groups but are uncommon in adolescents. They are most likely to occur in women over 35.

As far as is known, phyllodes tumors occur with the same frequency in women of all races and in all parts of the world.

Causes & symptoms

The cause of phyllodes tumors is not known as of the early 2000s.

The symptoms of a phyllodes tumor include the rapid but painless growth of a smooth, bulky mass within the affected breast. The patient may notice that her entire breast is enlarged and its shape distorted. The skin overlying the tumor may feel warm to the touch and develop a shiny appearance; it may also become translucent.

Patients with metastases from a malignant phyllodes tumor may experience difficulty breathing (dyspnea), **bone pain**, and **fatigue**.

Diagnosis

The diagnosis of a phyllodes tumor may be made when the patient notices a rapidly growing mass in her breast and consults her doctor. After palpating (feeling) the mass and evaluating the appearance of the overlying skin, the doctor will order **imaging studies** and an open breast **biopsy**. Although a mammogram or ultrasound study may be useful in evaluating the size and location of the tumor, these tests are not reliable in distinguishing among benign phyllodes tumors, fibroadenomas, and malignant phyllodes tumors. In addition, fine-needle aspiration does not usually confirm the diagnosis; an open biopsy is considered the definitive diagnostic test as of the early 2000s.

There are no tumor marker or other blood tests that can be used to diagnose phyllodes tumors as of 2005.

Treatment team

The treatment team for a patient with a phyllodes tumor will usually include a diagnostic radiologist, a gynecologist, a general surgeon, and a pathologist.

Clinical staging, treatments, and prognosis

Staging

Phyllodes tumors are not staged in the usual sense; they are classified on the basis of their appearance under the microscope as benign, borderline (or indeterminate), or malignant. The pathologist makes the decision on the basis of the cells' rate of division (mitosis) and the number of irregularly shaped cells in the biopsy sample. In one series of 101 patients with phyllodes tumors, 58 percent were identified as benign, 12 percent as borderline, and 30 percent as malignant.

Treatments

Surgical excision (removal) is the usual treatment for phyllodes tumors, whether benign or malignant. In the case of benign tumors, the surgeon will usually try to spare as much breast tissue as possible, generally removing about 1 in (2 cm) of normal breast tissue from the

area around the tumor as well as the tumor itself. If the tumor is very large, however, the doctor may remove the entire breast.

In the case of malignant tumors, the surgeon will remove a wider area of normal tissue along with the tumor—a technique known as wide local excision (WLE)—or perform a complete **mastectomy**.

Although **radiation therapy** has been tried as follow-up treatment after surgery, phyllodes tumors do not respond well to either radiotherapy or **chemotherapy** if they recur or metastasize. In addition, malignant phyllodes tumors do not respond to hormone therapy.

Prognosis

The prognosis for benign phyllodes tumors is good following surgical removal, although there is a 20–35 percent chance of recurrence, particularly in patients over the age of 45. Recurrence is usually treated with further surgery, either another local excision or a complete mastectomy.

The prognosis for patients diagnosed with borderline or malignant phyllodes tumors is more guarded. About 4 percent of borderline tumors will eventually metastasize. A Mayo Clinic study of 50 patients with malignant tumors found that 32 percent had a recurrence within two years after surgery; 26 percent developed metastases, and 32 percent of the group died from their malignancy. The most common sites for metastases from malignant phyllodes tumors are the lungs, bones, liver, and chest wall, although metastases to the lymph nodes have also been reported. Most patients with metastases from a malignant phyllodes tumor die within three years of their first treatment.

Alternative and complementary therapies

Women who have had surgery for removal of a phyllodes tumor appear to use CAM therapies as often and for the same reasons as women treated for **breast cancer**. According to the Behavioral Research Center of the American Cancer Society, breast cancer survivors are highly likely to use some form of alternative or complementary therapy during cancer treatment or within a year or two of completing conventional treatment. A survey of 608 longer-term (8 years or longer) breast cancer survivors reported in early 2005 that the majority were still using CAM therapies. The survey respondents gave four reasons for using alternative treatments:

- To maintain an active role in recovery from cancer.
- To reduce their stress level.
- To reduce the risk of recurrence.
- To maintain hope.

KEY TERMS

Areola—The darkened ring of skin surrounding the nipple.

Fibroadenoma—A benign tumor derived from glandular tissue that contains fibrous tissue as well. Phyllodes tumors are sometimes referred to as giant fibroadenomas of the breast.

Mitosis—The process of cell division. The rate of mitosis in a tissue sample is one measurement used to determine whether a phyllodes tumor is benign or malignant.

Pathologist—A doctor who examines biopsy specimens and tissues removed during surgery for evidence of changes caused by disease.

Stroma—The supporting connective tissue of the breast or other organ.

Specific CAM therapies mentioned by the women in the ACS survey included exercise, humor, self-help books (bibliotherapy), prayer or spiritual practice, vitamin treatments, relaxation exercises, and support groups. Dr. Kenneth Pelletier, the former director of the program in complementary and alternative medicine at Stanford University School of Medicine, lists hypnosis, visualization, naturopathy, and journaling as other alternative approaches that breast cancer patients find helpful. Acupuncture is frequently mentioned as a useful method of pain control.

Coping with treatment

Coping with the aftereffects of surgery for a phyllodes tumor is similar to coping with the effects of surgery for breast cancer. Patients who have had a complete mastectomy may experience pain, limited range of motion or weakness in the affected arm, scarring, or swelling. Exercises, outpatient physical therapy, and massage help to relieve these side effects of breast surgery. In terms of follow-up, most patients treated for phyllodes tumors are scheduled for a postoperative visit with the surgeon 1–2 weeks after surgery, with periodic checkups thereafter.

Clinical trials

The National Cancer Institute (NCI) is not conducting any **clinical trials** involving phyllodes tumors as of 2005. There is, however, an ongoing study at the Dartmouth-Hitchcock Medical Center in New Hampshire of the effectiveness of radiation therapy in preventing

QUESTIONS TO ASK YOUR DOCTOR

- What are the chances that my phyllodes tumor is either borderline or malignant?
- What are the chances of a recurrence?
- Would you recommend a total mastectomy rather than local excision to minimize the risk of recurrence?

recurrences of borderline or malignant phyllodes tumors in patients who have been treated with local excision of the tumor. Women who have had a borderline or malignant phyllodes tumor removed within the past three months may wish to consider participating in this study.

Prevention

There is no way to prevent phyllodes tumors as of the early 2000s because their cause is not yet known.

Special concerns

The special concerns of patients with phyllodes tumors are similar to those of patients diagnosed with breast cancer, particularly concern about disfigurement, physical weakness, or recurrence if the entire breast has been removed.

See also Breast cancer; Fibroadenoma.

Resources

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ORGANIZATIONS

Behavioral Research Center, American Cancer Society. 1599 Clifton Road NE, Atlanta, GA 30329. (800) 758-0227 or (404) 329-7772. <http://www.cancer.org>.

Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center. One Medical Center Drive, Lebanon, NH 03756. (603) 653-9000. <http://www.cancer.dartmouth.edu>.

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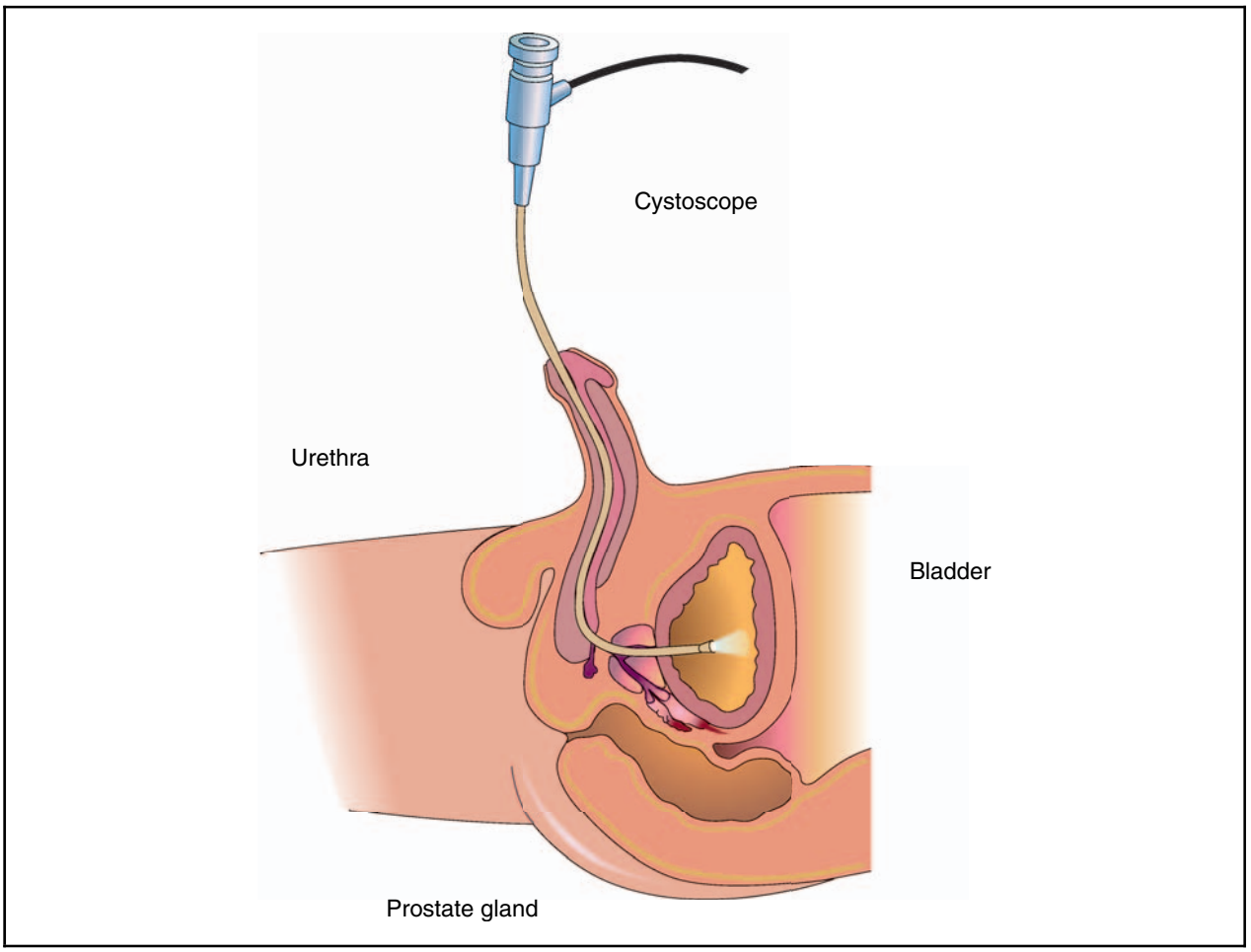
Rebecca Frey, PhD

Cystoscopy

Definition

Cystoscopy (cystourethroscopy) is a diagnostic procedure that is used to look at the bladder (lower urinary tract), collect urine samples, and examine the prostate gland. Performed with an optic instrument known as a cystoscope (urethroscope), this instrument uses a lighted tip for guidance to aid in diagnosing urinary tract disease and prostate disease. Performed by a urologist, this surgical test also enables biopsies to be taken or small stones to be removed by way of a hollow channel in the cystoscope.



Cystoscopy is a diagnostic procedure which is used to view the bladder, collect urine samples, and examine the prostate gland. This procedure also enables biopsies to be taken. The primary instrument used in cystoscopy is the cystoscope, a tube which is inserted through the penis, into the urethra, and ultimately into the bladder. *(Illustration by Electronic Illustrators Group.)*

Purpose

Categorized as an endoscopic procedure, cystoscopy is used by urologists to examine the entire bladder lining and take biopsies of any areas that look questionable. This test is not used on a routine basis but may benefit the urologist who needs further information about a patient who displays the following symptoms or diagnosis:

- blood in the urine (also known as hematuria)
- incontinence, or the inability to control urination
- a urinary tract infection
- a urinary tract that display signs of congenital abnormalities
- tumors located in the bladder
- the presence of bladder or kidney stones
- a stiffness or strained feeling of the urethra or ureters
- symptoms of an enlarged prostate

Blood and urine studies, in addition to x rays of the kidneys, ureters, and bladder may all occur before a cystoscopy. At the time of the procedure, a retrograde pyelogram may also be performed. Additional blood studies may be needed immediately following cystoscopy.

Precautions

While the cystoscopy procedure is commonly relied on to gather additional diagnostic information, it is an invasive surgical technique that may involve risks for certain patients. Those who are extremely overweight (obese), smoke, are recovering from a recent illness, or are treating a chronic condition may face additional risks from surgery.

Surgical risk also increases in patients who are currently using certain drugs including antihypertensives; muscle relaxants; tranquilizers; sleep inducers; insulin;

KEY TERMS

Cystoscopy with bladder distention (hydrodistention)—Under anesthesia, the bladder is stretched to capacity (distended) with either liquid or gas and then examined with a cystoscope. The examination will detect bladder wall inflammation; thick, stiff bladder wall; Hunner's ulcers; and glomerulations.

Endoscopy—Examination of body organs or cavities through the use of an endoscope (a lighted optical instrument used to see inside body cavities), such as a cystoscope used to complete a cystoscopy.

Glomerulation—Pinpoint bleeding caused by recurrent irritation that can appear on the bladder wall.

Retrograde pyelogram—A pyelography or x-ray technique in which radiopaque dye is injected into the kidneys from below, by way of the ureters, allowing further examination of the kidneys.

Ureter—The tube that carries urine from the kidney to the bladder, with each kidney having one ureter.

Urethra—A passageway from the bladder to the outside for the discharge of urine. In the female this canal lies between the vagina and the clitoris; in the male the urethra travels through the penis, opening at the tip.

sedatives; beta blockers; or cortisone. Those who use mind-altering drugs also put themselves at increased risk of complications during surgery. The following mind-altering drugs should be avoided: narcotics, psychedelics, hallucinogens, **marijuana**, sedatives, hypnotics, or cocaine.

Description

Depending on the type of information needed from a cystoscopy, the procedure typically takes 10–40 minutes to complete. The patient will be asked to urinate before the procedure, which allows an accurate measurement of the remaining urine in the bladder. A well-lubricated cystoscope is inserted through the urethra into the bladder, where a urine sample is taken. Fluid is then pushed in to inflate the bladder and allow the urologist to examine the entire bladder wall.

During an examination, the urologist may take the following steps: remove either bladder or kidney stones; gather tissue samples; and treat any suspicious lesions. In order to perform the x-ray studies known as a retrograde pyelogram, a harmless dye is injected into the ureters by way of a catheter that is passed through the previously placed cystoscope. After completion of all needed tests, the cystoscope is removed.

Preparation

A cystoscopic procedure can be completed in a hospital, a doctor's office, or an outpatient surgical facility. An injection of spinal or general anesthetic may be used prior to a cystoscopy. Although this test is typically performed on an outpatient basis, a patient may require up to three days' recovery in the hospital.

Aftercare

Patients who have undergone a cystoscopy will be instructed to follow these steps to ensure a quick recovery:

- Because of soreness or discomfort that may occur in the urethra, especially while urinating, several warm baths a day are recommended to relieve any pain.
- Allow four days for recovery.
- Be aware that blood may appear in the urine. This is common and soon clears up in one to two days following the procedure.
- Avoid strenuous exercise for a minimum of two weeks following cystoscopy.
- Sexual relations may continue when the urologist determines that healing is complete.
- Wait at least two days after surgery before driving.

Patients may also be prescribed pain relievers and **antibiotics** following surgery. Minor pain may also be treated with over-the-counter, nonprescription drugs such as acetaminophen.

Risks

As with any surgical procedure, there are some risks involved with a cystoscopy. Complications may include profuse bleeding, a damaged urethra, a perforated bladder, a urinary tract infection, or an injured penis.

Patients should also contact their physician if they experience any of the following symptoms following surgery: pain at or redness or swelling around the surgical site; drainage or bleeding from the surgical site; signs of infection, which may include headache, muscle aches, dizziness, an overall ill feeling, and **fever**; nausea or vomiting; strenuous or painful urination; or symptoms that may result as side effects from the medication.

QUESTIONS TO ASK THE DOCTOR

- Why do I need a cystoscopic examination?
- How long will a cystoscopic procedure take?
- How long is recovery from a cystoscopic procedure?

Normal results

A successful cystoscopy includes a thorough examination of the bladder and collection of urine samples for cultures. If no abnormalities are seen, the results are indicated as normal.

Abnormal results

Cystoscopy allows the urologist to detect inflammation of the bladder lining, prostatic enlargement, or tumors. If these are seen, further evaluation or biopsies may be needed, in addition to the removal of some tumors.

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Road, NE, Atlanta, GA 30329-4251. (800)ACS-2345. http://www.cancer.org/ .The American Cancer Society (ACS) is a nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem and is the largest source of private, nonprofit cancer funds. The ACS hopes to prevent cancer, save lives, and diminish suffering from cancer through research, education, advocacy, and service.

Interstitial Cystitis Association (ICA). 51 Monroe Street, Suite 1402, Rockville, MD 20850. 1-800-HELP-ICA. http://www.ichelp.org. Founded in 1984, the ICA is a not-for-profit health organization dedicated to providing patient and physician educational information and programs, patient support, public awareness, and research funding.

National Institute of Diabetes & Digestive & Kidney Disease. Office of Communications and Public Liaison, NIDDK, NIH, 31 Center Drive, MSC 2560, Bethesda, MD 20892-2560. NIDDK_Inquiries@nih.gov. http://www.niddk.nih.gov. Mission to understand, treat, and prevent diseases, such as diabetes and obesity, digestive diseases such as hepatitis and inflammatory bowel disease, kidney and urologic diseases such as kidney failure and prostate enlargement, and blood diseases such as the anemias.

National Kidney and Urologic Diseases Information Clearinghouse. 3 Information Way, Bethesda, MD 20892-3580. 1-800-891-5390. nkudic@info.niddk.nih.gov. http://www.niddk.nih.gov/health/kidney/nkudic.htm. Knowledge and understanding about diseases of the kidneys and urologic system among people with these conditions and their families, health care professionals, and the general public.

Beth A. Kapes

Cytarabine

Definition

Cytarabine (also known as ARA-C, and by the brand name Cytosar) is an anticancer agent that kills cancer cells. It is very frequently used with other anticancer drugs in the treatment of **acute myelocytic leukemia** (AML), lymphomas, and for leukemia and **lymphoma** affecting the surrounding membranes of the brain and spinal cord (meninges).

Purpose

There are two formulations of this drug: cytarabine, and cytarabine liposomal, where the drug is encapsulated in a molecule of lipid. Cytarabine is used to treat acute myelogenous leukemia, **acute lymphocytic leukemia** (ALL), **chronic myelocytic leukemia** (CML), central nervous system (CNS) leukemia affecting the membrane surrounding the brain and spinal cord, and Hodgkin's and non-Hodgkin's lymphoma (NHL). Cytarabine liposomal (brand name Depocyt) is primarily used to treat lymphoma involving the meninges (the membrane covering the brain and spinal cord).

Description

Cytarabine is a cytotoxic drug. This means that its task is to kill cancer cells. Cytarabine kills cells by interfering with the production of DNA.

KEY TERMS

Cytotoxic drug—A medicine that kills (cancer) cells.

DNA—An acid found in all living cells that contains tiny bits of genetic information.

Lipids—Substances including fats, waxes, and related compounds that (with proteins and carbohydrates) constitute the principal structural components of living cells.

Recommended dosage

The dose for cytarabine may be different depending on the protocol used by the physician. An example dose of cytarabine is 100 to 200 mg per square meter of body surface area per day for seven days as an intravenous (IV) medication.

High-dose cytarabine may be 2 to 3 grams per square meter of body surface area twice a day for three days. Cytarabine is also administered directly into the cerebral spinal fluid for lymphoma or leukemia involving the meninges. The dose is 5 to 75 mg per square meter of body surface area every two to seven days. The dose for cytarabine liposomal in the cerebral spinal fluid is usually 50 mg.

Precautions

Liposomal cytarabine not be given to patients with infections of the meninges, allergic reaction to cytarabine, or if the patient is pregnant.

Side effects

Side effects include **fever** in greater than 80% of patients, hair loss (alopecia), nausea and vomiting, **diarrhea**, ulcers of the mouth, decreased white blood cells (responsible for fighting infections), decreased platelets (responsible for blood clotting), decreased red blood cells (responsible for oxygenation of tissues), and decrease in liver function. Abdominal pain, loss of appetite, and a metallic taste in the mouth may develop, as may an allergic reaction. Tearing, eye pain, foreign body sensation in the eye, blurred vision, and sensitivity of the eyes to light occurs with high-dose cytarabine and may be prevented or relieved with corticosteroid eyedrops. Patients receiving high-dose cytarabine may also experience skin sloughing, redness and pain of the palms of the hand and soles of the feet, dizziness, headaches, drowsiness, confusion, personality changes, abnormal movements of the eye, loss of coordination, and in severe cases, loss of consciousness.

Although it is uncommon, one of the most serious side effects of cytarabine may involve sudden respiratory distress involving abnormal, shallow, and rapid breathing, which may progress to **pneumonia**.

High doses of cytarabine may trigger what is known as cytarabine syndrome, which consists of fever, muscle ache, **bone pain**, occasional chest pain, rash, inflammation of the membrane that covers the outer surface of the eye. This syndrome occurs six to 12 hours after the drug is given. **Corticosteroids** can treat this syndrome or prevent it from occurring.

Interactions

Drugs that decrease the function of the kidneys may increase the toxic side effects of cytarabine. Cytarabine may decrease the effect of digoxin and the **antibiotics** gentamicin and flucytosine. Prior to starting any new medications or herbal remedies, patients should consult with their physician, nurse, or pharmacist to prevent any drug interactions.

Bob Kirsch

Cytogenetic analysis

Definition

Cytogenetics is the analysis of blood or bone marrow cells that reveals the organization of chromosomes. Chromosomes are the physical structures that contain the genetic material, DNA.

Purpose

Cytogenetic analyses are essential to the diagnosis and treatment of different forms of cancer, especially leukemia, cancers of the blood cell-forming system. The results of cytogenetic tests can help to confirm the diagnosis of a particular form of leukemia, and permit the best treatment to be selected for each patient.

Precautions

This test is performed on tissue or cells that have been removed during the initial surgery or diagnostic procedure used to determine the precise nature of the leukemia or other cancer. It usually does not require any

KEY TERMS

Chromosome—The self-replicating genetic the structures in cells that containing the cellular DNA, the hereditary material, that includes the genes in a particular order.

DNA sequence—The relative order of nucleotides, the chemical subunits of a DNA molecule.

Gene rearrangement—A change in the structure of a chromosome that changes the order of genes.

Karyotype—A complete set of chromosomes that are examined to look for genetic abnormalities

QUESTIONS TO ASK THE DOCTOR

- Are the cytogenetic results what you would expect based upon other diagnostic tests and examinations I have undergone?
- Will you want to repeat this test? At what point in my treatment will you want to do so?
- Do these test results tell you anything about my prospects for a disease-free survival?

new surgery or blood draw on the patient and, so, does not entail any additional precautions for the patient.

Description

The development of leukemia and other cancers involves alterations, or mutations, in the cellular genetic material. The types of changes seen differ among various forms of cancer, but include changes in the specific sequence of DNA substituent units (termed nucleotides), as well as more dramatic alterations. Some of these more dramatic alterations include loss or duplication of large stretches of DNA sequence, or chromosomal rearrangements that correspond to the movement of genetic sequences from one chromosome to another. These rearrangements can lead to the production of novel, and often characteristic, molecules that are believed to play essential parts in the development of particular cancers.

Cytogenetic analysis focuses upon chromosomal rearrangements. In essence, this type of testing is a hybrid approach that combines genetics, analysis of mutations, with examination of cells. The cells to be tested, usually obtained from circulating blood or bone marrow, are treated in such a way that the chromosomes are made visible. Cells that are about to divide and which have condensed and organized their chromosomes into pairs are most suitable for this type of analysis. Often cells will be treated in the laboratory to increase the frequency of such cells, in which the chromosomes are visible as what are called mitotic figures. Cells containing such mitotic figures are then chemically stained in a way that makes it possible to identify specific chromosomes. When such stained chromosomes are visualized and enumerated, the resulting pattern is termed the karyotype of that cell.

The karyotypes of many cells are usually scrutinized to establish whether some fraction of cells display a reproducible genetic alteration that can be associated with a specific cancer. Historically, the first such abnormality recognized was the Philadelphia chromosome, which is associated with chronic myelogenous leukemia (also called **chronic myelocytic leukemia**, or CML). In virtually all cases of CML, cytogenetic analyses will reveal a Philadelphia chromosome. The presence of this marker can be used to monitor response to treatment. There are a variety of other genetic abnormalities that are associated with specific forms of cancer. Most of these have been recognized using cytogenetics, and to varying degrees have become useful in diagnosis of leukemia and solid tumors, or in predicting treatment outcome.

Cytogenetics examines microscopically visible chromosomal changes. More recently developed molecular approaches can recognize the same sorts of genetic rearrangements as seen in abnormal karyotypes. In addition, these molecular tests can recognize smaller, more subtle alterations affecting just one or a few of the nucleotide units within a cancer-related gene. These techniques can, in some cases, be more sensitive than cytogenetic approaches, and along with the large body of information derived from the human genome project, hold the promise or providing more accurate tests for diagnosis and treatment of cancer.

Preparation and Aftercare

The only preparation and aftercare would be the preparation and aftercare required for the sample collection—a blood draw or a **bone marrow aspiration and biopsy**. The cytogenetic analysis itself requires no additional preparation or aftercare on the part of the patient.

Risks

This test is performed on tissue or cells that have been removed during the initial surgery or diagnostic procedure used to determine the precise nature of the

leukemia or other cancer. It usually does not require any new surgery or blood draw on the patient and, so, does not entail any additional risk to the patient.

Results

Human body cells, exclusive of reproductive cells, have 23 pairs of chromosomes. Any deviation from this is considered abnormal. Cytogenetic analysis directed toward leukemia or other cancer cells is considered to have an abnormal result when a specific, distinctive genetic alteration is seen in the configuration of these chromosomes. The absence of a cytogenetic alteration is not, by any means, a basis to conclude there is an absence of a particular disease or that the prognosis is better than if a genetic abnormality was observed. For example, in **acute lymphocytic leukemia** (ALL) there are several different genetic rearrangements that are each associated with a different outcome. The patients who do the best are not those without any cytogenetic abnormality, but rather those with one specific chromosomal rearrangement. Therefore the potential use of cytogenetics, and similar molecular analyses, is to enable doctors to more accurately determine the diagnosis, treatment, and follow-up of patients with leukemia and other forms of cancer.

See also Chromosome rearrangements.

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Warren Maltzman, Ph.D.

Cytology

Definition

Cytology is the examination of individual cells and small clusters of cells, and may be used for the diagnosis and screening of diseases, including cancers. Cytology also refers to the study of diseases at the cellular level. For diagnosing diseases such as cancer, cytology may be referred to as cytopathology.

Purpose

Diagnostic tests are used to detect a disease in individuals who have signs, symptoms, or some other abnormality that indicates a disease. A **screening test** identifies those who might have a certain disease, sometimes before they develop any symptoms, but does not absolutely prove the disease is present. If a screening test is positive, a diagnostic test can be used as follow-up to verify the diagnosis.

Researchers at binocular light microscopes analyze biological samples in a laboratory. The samples have been prepared on glass slides in trays and have been stained with dyes to highlight certain types of cells or tissues. *(Copyright CC Studio, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Precautions

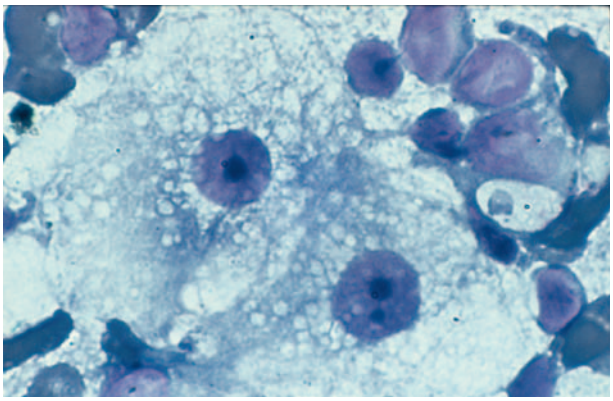
Procedures to gather cells for cytology are often less invasive than other forms of **biopsy**, and therefore may cause less discomfort, be less likely to result in serious complications, and cost less to perform. In some situations, however, where a piece of tissue is removed rather than individual cells, a different type of biopsy may be required to confirm the cytologic diagnosis.

Description

Samples for cytology can be obtained in more than one way. Fine needle aspiration (FNA) is a type of biopsy in which tumor samples are taken through thin needles.

Scrape or brush cytology is another technique in which cells are scraped or brushed from the organ or tissue being tested. Samples from the esophagus, stomach, bronchi (breathing tubes that lead to the lungs), mouth, and cervix (Pap smear) can be obtained using this type of procedure.

Liquid-based cytology has been introduced in Great Britain as an alternative to the scrape method for collecting cervical cells for Pap smears. It is considered more comfortable and as effective by those who have introduced the method.



Kidney cancer cells for examination by a pathologist. *(Copyright Parviz M. Pour, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

KEY TERMS

Biopsy—Removing tissue from living patients for a diagnostic examination.

Cytology/cytopathology—The study of cells or cell types.

Fine needle aspiration—Removal of tissue or suspensions of cells using a small needle.

Pap smear—A common cytology test used to screen for malignant and premalignant changes of the cervix.

How a cytology sample is processed depends on what type of sample it is. A doctor can smear a sample directly on a glass microscope slide. The slide is then stained and viewed by a cytopathologist. In other cases, the fluid is concentrated before being smeared and stained on a slide. This is especially useful for dilute samples such as those from body cavities.

Most routine cytology results are available one or two days after the sample is received in the laboratory. There are many reasons why some results take longer to return, such as if special stains are required to confirm a diagnosis.

Preparation, Aftercare, and Risks

Cytology analysis is performed on cells gathered during diagnostic procedures. The preparation, aftercare, and risks depend on the procedure used to gather the cells.

Normal results

A cytopathologist examines the cells through a microscope and identifies the normal and abnormal cells on the slide using a microscope. Normal results generally indicate no sign of cancer.

QUESTIONS TO ASK THE DOCTOR

- What is a cytology test?
- How accurate is a cytology test?
- How long will it take to get cytology test results?

Abnormal results

A cytopathologist examines the cells through a microscope. Abnormal cells may show signs that point to a possible diagnosis of cancer.

See also Biopsy; Pap test.

Resources

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American Society for Clinical Pathologists (ASCP). 2100 West Harrison Street, Chicago, IL 60612. (312) 738-1336. <http://www.ascp.org.>.

American Society for Cytopathology (ASC). 400 West 9th Street, Suite 201, Wilmington, DE 19801. (302) 429-8802. <http://www.cytopathology.org.>.

College of American Pathologists (CAP). 325 Waukegan Road, Northfield, IL 60093. (800) 323-4040. <http://www.cap.org>.

International Academy of Cytology (IAC). 1640 East 50th Street, Ste. 20C, Chicago, IL 60615-3161. (773) 955-1406. <http://www.cytology-iac.org>.

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Cytopenias *see* **Neutropenia and Thrombocytopenia**

D

Dacarbazine

Definition

Dacarbazine, also known as DTIC-Dome or DTIC, is an anticancer agent best known for its long-time use in treating metastatic malignant **melanoma**.

Purpose

Dacarbazine has been approved by the Federal Drug Administration (FDA) for use in the treatment of metastatic malignant melanoma and Hodgkin's lymphoma, as well as other neoplasms.

Metastatic malignant melanoma

Dacarbazine used alone produces a response in up to 25% of patients with **metastasis** to the surrounding skin and lymph nodes. Though it has been studied in combination with other drugs, and some three-drug combinations (such as CVD, or cisplatin, vincristine, and dacarbazine) have shown promise, evidence thus far does not indicate a clear advantage over traditional single-agent treatment with dacarbazine. Some reserchers have treated patients with a four-drug regimen known as BVLD, for bleomycin, vincristine, lomustine, and dacarbazine. Again, however, this regimen has not been found to be clearly superior to monotherapy with dacarbazine.

Dacarbazine is sometimes given as palliative therapy for disseminated malignant melanoma. Palliative therapy is treatment that is given to relieve symptoms when a cure is no longer possible.

Hodgkin's disease

In **Hodgkin's disease**, dacarbazine is indicated as a second-line therapy, meaning it is used after initial therapies have failed or if the patient's disease recurs. It is usually used in conjunction with other drugs, most commonly in a regimen called "ABVD," which is comprised of the drugs **doxorubicin** (Adriamycin), **bleomycin**, **vinblastine** and dacarbazine. ABVD has produced complete remission in up to 70% of cases.

Other neoplasms

Dacarbazine has other, unlabeled uses. It has been used to treat soft tissue **sarcomas** and malignant metastatic pheochromocytomas. When used with other **chemotherapy** agents, it has also shown to have some activity in the treatment of non-small cell lung cancer.

Description

Dacarbazine is a non-classical alkylating agent that causes DNA mispairing and strand breakage, leading to cell death (necrosis). Its exact mechanism is not completely understood. It is a cell cycle nonspecific drug, meaning that it causes cell damage and death throughout the life cycle of a cell, and not at any one particular time. When a patient is treated with dacarbazine 50% of the drug is metabolized by the liver, and 50% excreted in urine.

Recommended dosage

Dacarbazine comes in a vial, and must be mixed with sterile water according to manufacturer instructions prior to administration. It may be given directly into a vein, slowly, or by infusion over a time period of 15 minutes to an hour. Safety and effectiveness of this drug have not yet been established in children.

Chemotherapy dosages are usually based on a person's body surface area (BSA), which is calculated in square meters using height and weight measurements. Drug dosages are ordered in milligrams per square meter (mg/m^2). In some cases, chemotherapy may be ordered in milligrams per kilogram body weight. (One kilogram equals 2.2046 pounds.)

There are three regimens that may be considered when prescribing dacarbazine for metastatic malignant melanoma: the ten-day, five-day, and one-day regimen. The

dosages recommended are as follows: 2-4.5mg/kg/day for ten days, repeated every four weeks; 250mg/square meter/day every five days, and repeated every three weeks; and 850-1000mg/square meters for one day, repeated every three weeks. Because of recently developed drugs called 5HT3 **antiemetics** that treat **nausea and vomiting**, the one-day regimen is currently the most commonly used. To date, no studies have indicated that schedule or daily dose affects response rates.

Dacarbazine is usually given in combination with other drugs in the treatment of Hodgkin's lymphoma. The recommended dosage is 150mg/square meter, given once a day for five days. Treatment is repeated every four weeks. Alternatively, the drug may be given on only the first day of treatment, and every 15 days thereafter. For this regimen, the recommended dose is 375mg/square meter.

Precautions

Anaphylaxis is rarely associated with dacarbazine. Dacarbazine should not be used in patients who have demonstrated previous sensitivity to it.

Dacarbazine is classified as both an irritant, meaning that the drug has the potential to cause pain and inflammation at the site if it seeps out of the vein and into the surrounding tissue. Should this event, called extravasation, occur, hot packs should be applied. Rarely, extravasation of dacarbazine results in tissue damage or death.

Animal studies have indicated that dacarbazine may be carcinogenic and damaging to an unborn fetus It should be used only when the need outweighs the risks There have not been adequate studies to determine whether it does pass to the milk. To be safe, women undergoing treatment with dacarbazine should not breast-feed.

Side effects

Hematopoietic

The most common side effect of dacarbazine is moderate bone marrow suppression. White blood cells and platelets are most affected, though red blood cells may also be decreased. These effects are potentially life threatening, requiring frequent blood level monitoring, and potentially a decrease or complete cessation of the drug. These effects may be delayed from two to four weeks after the drug is administered. Patients should be monitored for symptoms of low white blood cell count. Symptoms may include sore throat, burning during urination, **diarrhea**, or **fever**. Symptoms of low platelet count may include bleeding, increased bleeding with menstruation, and unexplained bruising. Symptoms of **anemia** may include dizziness, **fatigue**, and/or pallor.

Gastrointestinal

Dacarbazine is a highly emetogenic drug, meaning it frequently causes nausea and/or vomiting. Symptoms begin after one to six hours of administration, and can last up to five days. However, with appropriate supportive care, dacarbazine is usually well tolerated. Preventing nausea and vomiting can usually be accomplished by administering antiemetic medications before dacarbazine is administered, and even up to several days afterwards. There are several regimens available. In addition, restricting food intake for several hours prior to the administration of the drug can help reduce adverse gastrointestinal effects.

Cardiovascular

Dacarbazine has been associated with episodes of low blood pressure that resolve when the drug is stopped. Dacarbazine is prepared in vials with citric acid and the drug mannitol. There is some consideration that these hypotensive episodes may be related to the citric acid, and not the dacarbazine itself.

Dermatological

Although photosensitivity (sensitivity to sunlight) is rare, patients should be instructed to avoid sun exposure after treatment. When outdoors, patients should wear sunscreen and protective clothing. Reactions may include redness, swelling and/or **itching** of the skin. In more serious cases, blisters may develop.

Dacarbazine may also affect the skin in other ways. For example, it may cause hyperpigmentation of the nails. When used in conjunction with the drugs doxorubicin, bleomycin, and vinblastine, dacarbazine can cause brown streaks to form over the sites of infusion. Dacarbazine may also cause flushing, a temporary redness of the face, neck and chest area. Dacarbazine can also cause hair loss, although uncommon. Once treatment stops, hair growth nearly always recurs.

Other

Dacarbazine is sometimes associated with a flu-like syndrome that causes fatigue, muscle aches, and sometimes an increased temperature. Reportedly, symptoms begin about a week after therapy, and resolve within one to three weeks. Rarely, dacarbazine causes liver toxicity, symptoms of which may include yellowing of the whites of the eyes or skin, abdominal pain and nausea.

Interactions

Dacarbazine is best administered in dextrose 5% water or normal saline. It should not be given with the following medications, as they are chemically incompa-

KEY TERMS

Antiemetic—A drug that prevents or alleviates nausea and vomiting.

Body surface area—A measurement based on height and weight that is calculated in square meters. It is used to determine chemotherapy dosages.

Carcinogenic—A substance capable of causing cancer.

Disseminated—Spread throughout the body.

Extravasation—Passage or leakage from a blood vessel into the surrounding tissue.

Hematopoietic—Referring to proteins that cause growth and maturity in blood cells.

Monotherapy—Treatment of a disease or disorder with the use of a single drug.

Myelosuppression—Suppression of bone marrow function that results in decreased platelets, red blood cells, and white blood cells.

Palliative therapy—Treatment given to relieve the symptoms of a disease rather than to cure it.

tible: **allopurinol** sodium, cefepime HCl, **Heparin** sodium, or piperacillin sodium. Patients should let their doctors know what medications they are taking, as there may be some adverse reactions. Patients at risk for bone marrow suppression, such as those taking dacarbazine, should avoid aspirin-containing medicines as they may increase the risk of bleeding.

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United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA (463-6332). <http://www.fda.gov>.

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Daclizumab

Definition

Daclizumab is a humanized monoclonal antibody of the IgG1 type produced by recombinant DNA technology that binds to a specific interleukin-2 (IL-2) receptor known as CD25 or Tac. This receptor is expressed on the surface of cancerous lymphocytes in a number of blood malignancies. Daclizumab has also been known as dacliximab and is marketed in the United States under the Zenapax brand name.

Purpose

When used against cancer, this drug is intended to stop the growth of blood cell (hematologic) cancers that express the CD25 protein on the surface of the cancerous cells. Some representative cancers include adult T-cell leukemia/lymphoma (ATL), **hairy cell leukemia** (HCL), **cutaneous T-cell lymphoma** (CTCL), chronic lymphocytic lymphoma (CLL), **Hodgkin's disease**, non-Hodgkin's lymphoma (NHL), and other peripheral T-cell or lymphoid leukemias or lymphomas.

Based on the antibody's known ability to block IL-2 binding experimentally, this drug would be expected to work most effectively at the times that the cancerous cells require IL-2 for growth. Generally, this is in the early stages of the disease. However, limited clinical evidence and some experimental evidence support an as of yet uncharacterized alternative method of action that may work during the later, IL-2 independent stages of the cancers.

Description

Daclizumab is a genetically engineered monoclonal antibody that was approved by the FDA in late 1997 as an immunosuppressive drug for use in kidney

transplantation. The use of this drug in transplantation is based on the known interaction of activated lymphocytes with IL-2 during the rejection of transplanted tissue. It has not yet been approved for use as a cancer therapy. As of mid-2001 there were at least three active **clinical trials** to test the ability of daclizumab to treat hematologic cancers. The drug has also been used experimentally to treat IL-2-mediated autoimmune diseases such as uveitis and tropical spastic paraparesis.

Monoclonal antibodies are proteins of the immune system that bind specifically to a particular antigen. Daclizumab was constructed to bind specifically to the alpha subunit of the IL-2 high affinity receptor, a protein also known as CD25 or Tac. By binding to the IL-2 receptor, it is theorized that daclizumab will block the action of IL-2 on the cell, whether it be uncontrolled growth or an uncontrolled immune reaction.

Fusion antibodies related to daclizumab have been developed and are being studied in clinical trials. One fusion antibody links the antibody with radioactive yttrium (Y 90), effectively bringing **radiation therapy** directly to the cancer cells. Another called LMB-2 fuses the antibody binding site with a bacterial exotoxin that is toxic to the cancer cells. This drug is the first recombinant immunotoxin to induce major responses in cancer during a clinical trial.

Most of the daclizumab sequence is derived from human sequences, while about 10% are from mouse sequences. The human sequences were derived from the constant domains of human IgG1 (called "constant" because it is essentially the same for all IgG antibodies) and the variable framework regions of a human antibody against an antigen seen on the surface of **myeloma** cells. These areas do not bind to the IL-2 receptor. Using human sequences in this part of the antibody helps to reduce patient **immune response** to the antibody itself and is called humanization. The actual binding site of daclizumab to the IL-2 receptor is from a mouse anti-Tac antibody.

Recommended dosage

Clinical trials are currently ongoing to determine the most effective dosage and treatment cycles for daclizumab against hematologic cancers.

Precautions

Daclizumab therapy on an outpatient basis requires regular visits to the doctor to check progress. Laboratory tests are needed to make sure daclizumab is working properly and not overly compromising immune function.

KEY TERMS

Antibody—A protective protein made by the immune system in response to an antigen, also called an immunoglobulin.

Exotoxin—A protein produced by a bacteria that is both toxic and produced an immune response by the host.

IgG—Immunoglobulin type gamma, the most common type found in the blood and tissue fluids.

Interleukin-2—A cytokine responsible for the activation of B and T cells of the immune system that induces growth and maturation.

Humanization—Fusing the constant and variable framework region of one or more human immunoglobulins with the binding region of an animal immunoglobulin, done to reduce human reaction against the fusion antibody.

Monoclonal—Genetically engineered antibodies specific for one antigen.

Because of the possible suppression of the immune system by this drug it is important to maintain good dental hygiene and see a dentist regularly. Also, because the drug would cross the placenta and the effects on an unborn child is unknown, effective contraception is necessary for women of childbearing age while receiving this medicine.

Side effects

Some uncommon side effects of daclizumab needing medical attention include chest pain; coughing; dizziness; **fever**; nausea; rapid heart rate; red, tender, oozing skin; shortness of breath; swelling of the feet or lower legs; trembling or shaking of the hands or feet; vomiting; weakness and, rarely, frequent urination.

Some also uncommon and less serious side effects include constipation; **diarrhea**; headache; heartburn; joint pain; muscle pain; slow wound healing and trouble in sleeping.

Interactions

The following medications have been administered in clinical trials with daclizumab with no increase in adverse reactions: **cyclosporine**, **mycophenolate mofetil**, ganciclovir, acyclovir, **azathioprine**, and **corticosteroids**. Daclizumab has also been used by small

numbers of patients without reaction with other immune suppressive drugs such as **tacrolimus**, **muromonab-CD3**, antithymocyte globulin, and antilymphocyte globulin.

See also Monoclonal antibodies.

Michelle Johnson, M.S., J.D.

Dactinomycin

Definition

Dactinomycin is a chemotherapeutic agent belonging to a family of medicines known as antineoplastic drugs. Alternative trade names or brand names for dactinomycin include Actinomycin-D and Cosmegen.

Description

Dactinomycin is one of the older **chemotherapy** drugs, having gained approval from the Food and Drug Administration (FDA) in 1982. This highly potent and effective cytotoxic agent is a mixture of substances produced by the bacteria *Streptomyces parvullus*. Its toxic properties prevent its use as an antibiotic.

Dactinomycin interferes with the growth of cancer cells by complexing with a cell's genetic material (deoxyribonucleic acid, or DNA). This prevents the cell from producing the proteins necessary to function and grow, thereby killing it. Dactinomycin may be used as a single chemotherapeutic agent or in conjunction with other antineoplastics (such as **vincristine** and **cyclophosphamide**) for greater efficacy.

Purpose

Dactinomycin is used in the treatment of **Ewing's sarcoma**, **Wilms' tumor**, **rhabdomyosarcoma**, gestational trophoblastic tumors, **Kaposi's sarcoma**, and soft tissue **sarcomas**. It is less commonly used for cancers of the uterus and testis.

Recommended dosage

The exact schedule and method of dactinomycin administration will be prescribed by an oncologist based on the type and stage of the cancer. An appropriate starting treatment regimen for adult patients is 500 mg/day for five consecutive days at two to four week intervals if the drug is tolerated. For children the dose is 15 mg/day over the same time course as prescribed for adults. Dactinomycin is not recommended for children less than one year of age; little clinical data is available on the use of dactinomycin in the elderly. Administration may be by intravenous (IV) injection, through a running IV infusion, or through a central line inserted under the skin into a vein near the collarbone.

Precautions

To maximize treatment effects, patients receiving dactinomycin should observe the following guidelines, as well as any modifications given by the oncologist:

- The area surrounding the injection site should be monitored.
- Patients should have regular laboratory testing for white blood cell count and kidney, liver, and bone marrow function.
- In order to reduce the possibility of immunosuppression, immunizations not approved or prescribed by the oncologist should be avoided.
- Patients should avoid contact with individuals taking or that have recently taken the oral polio vaccine, or individuals that have an active infection. When necessary a protective facemask should be worn.
- Oral hygiene procedures should be followed to reduce the risk of gum abrasion.
- Patients should not touch eye and nasal areas unless hands have been properly washed immediately prior to contact.
- To reduce bleeding and bruising complications, patients should exercise extreme caution when handling sharp instruments and decline participation in contact sports.
- Prior to treatment, the patient's medical history should be thoroughly reviewed to avoid complications that might arise from previous conditions such as gout, kidney stones, liver disease, chickenpox, shingles, or a history of allergic reactions to various drugs.
- The oncologist should be made aware if the patient is pregnant or if there is the possibility the patient might be pregnant, or if the patient is a breast-feeding mother.
- Only prescribed medications or over the counter (OTC) drugs approved by the oncologist should be taken by a patient receiving dactinomycin.

Side effects

Possible side effects of treatment with dactinomycin should be discussed with the patient prior to initiation of treatment. The patient should be instructed to notify the oncologist of any side effects. Side effects that may not

KEY TERMS

Antineoplastics—Agents that inhibit or prevent the maturation and proliferation of malignant cells.

Cytotoxic—Toxic to cells.

Ewing's sarcoma—A highly malignant primary bone tumor most often found in young adults under the age of 30.

Gestational trophoblastic cancer—A pregnancy associated cancer in which a grape-like mole develops in the uterus instead of a fetus.

Kaposi's sarcoma—A type of cancer associated with the skin and mucous membranes.

Myeloma—A malignant tumor composed of plasma cells normally found in the bone marrow.

Oncologist—A doctor who specializes in the diagnosis and treatment of patients with cancer.

Rhabdomyosarcoma—A malignant tumor derived from striated muscle.

Wilms' tumor—A cancerous tumor found in the kidneys of children.

be life threatening but give the patient cause for concern include hair loss (alopecia), intermittent **diarrhea**, **nausea and vomiting**, loss of appetite, difficulty swallowing, mouth sores or ulcers, and a general rash or change in skin tone. Side effects that should be reported immediately to the oncologist include unusual bleeding or bruising, black tarry stools, blood in the urine or stool, development of a cough, wheezing or hoarseness, **fever** or chills, lower back or side pain, painful or difficult urination, pinpoint red spots on the skin, and pain at the site of the injection. The oncologist will decide what type of intervention is best suited to control or extinguish the presented side effects, including changing the dosage, changing the treatment schedule, or discontinuing dactinomycin treatment.

Interactions

Certain medications should never be used together, but there are cases in which multiple drug treatment may be advisable even when drug interaction is well documented. Dactinomycin may be used in conjunction with other antineoplastic drugs or **radiation therapy** for increased efficacy of treatment. Under such conditions the oncologist will balance dosage and treatment schedules to maximize the positive effects of all drugs given and minimize any negative interactions.

It is essential that the oncologist be aware of any drugs that the patient is presently taking or has recently taken, or if the patient has recently received radiation therapy. A careful review of drugs that may interact with dactinomycin to lower its efficiency should be covered with the patient prior to treatment. These may include, but are not limited to, amphotericin B, antithyroid agents, **azathioprine**, chloramphenicol, flucytosine, ganciclovir, interferon, **plicamycin**, zidovudine, probenecid, and sulfinpyrazone.

See also Antineoplastic agents.

Jane Taylor-Jones, Research Associate, M.S.

Dalteparin *see* **Low molecular weight Heparin**

Danazol

Definition

Danazol is a synthetic androgen hormone that the Federal Drug Administration (FDA) approved in 1976. It is also known by its trade name, Danocrine.

Purpose

Danazol is approved for use in the treatment of endometriosis, fibrocystic breast changes, and in the prevention of hereditary angioedema. In addition, it has shown promise in the treatment of certain cytopenias.

Endometriosis

Endometriosis is a condition in which endometrial tissue, normally found in the uterus, implants itself in other areas of the body. The tissue continues to respond to hormones estrogen and progesterone during menstruation as it does in the uterus, but because the tissue cannot exit the body through the vagina during menstruation, it builds up, causing pain and inflammation. Danazol does not cure endometriosis, but renders the endometrial tissue located outside the uterus inactive. In most cases that are amenable to hormonal treatment, the endometrial lesions completely resolve, but can return within six months of stopping treatment.

Fibrocystic breast changes

Many women experience benign lumps or cystic changes in the breast. Most often, supportive bras and over-the-counter pain medication relieves symptoms.

However, in some women, pain and discomfort may be so great that medical treatment is warranted. Danazol is the only drug approved by the FDA for fibrocystic breast disease, and in this patient population usually results in complete resolution of nodularity and pain. However, symptoms usually return when medication is stopped.

Hereditary angioedema

Hereditary angioedema is a condition in which parts of the body, most dangerously the airway, develop episodic swelling. Danazol is used to prevent these rare, but potentially fatal, attacks.

Other

In addition to the aforementioned indications, there are other, unlabeled uses for danazol. The drug may be used to treat precocious puberty (premature sexual development), menorrhagia (excessively long menstrual periods), and gynecomastia (excess breast development in males).

Because it stimulates erythropoiesis (the production of red blood cells), it is sometimes administered to treat certain types of **anemia**. However, the use of danazol to combat anemia has declined since the recent developments in the synthetic production of erythropoeitin, a hormone naturally produced by the kidney that promotes the formation of red blood cells in bone marrow. In cancer patients, danazol may be used for its ability to stimulate erythropoiesis in individuals with types of **thrombocytopenia** (decreased platelets), often associated with HIV, or anemia. Danazol has shown promise in the management of autoimmune **hemolytic anemia**, a group of conditions in which the body produces antibodies that attack red blood cells. Myelodysplastic syndrome (MDS), a term that describes a group of hematologic cancers that often develop into **acute leukemia**, has shown some response to danazol treatment. However, more research is needed to better evaluate its potential in these patient populations.

Description

The pituitary gland produces hormones necessary for reproduction—follicle stimulating hormone (FSH) and luteinizing hormone (LH). Danazol suppresses the production of these and other hormones (estrogen and progesterone), inhibiting ovulation as a result. The effects are usually reversible. Approximately 60 to 90 days after treatment is stopped, ovulation and cyclic bleeding usually return.

Recommended dosage

The lowest therapeutic dose possible should be administered to minimize side effects. In some cases, doctors may periodically stop treatment or decrease dosages. In women, danazol should be started during menstruation or after tests to ensure the woman is not pregnant. Patients should be careful not to miss a dose, and if they do, should not take a double dose.

Endometriosis

Severe cases of endometriosis are initially treated with 800 milligrams (mg) of danazol, given in two divided doses. Gradually, the amount of medication is reduced to a level that is sufficient to suppress menstruation. Mild cases of endometriosis respond to lower doses of danazol. Typically, a doctor will first prescribe 200 to 400 mg a day, in two divided doses. Treatment should continue for three to six months, but in some cases, may last up to nine months.

Fibrocystic breast changes

Treatment for fibrocystic breast changes ranges from 100 to 400 mg given in two divided doses. Up to six months of danazol treatment may be needed to reduce breast nodularity and pain. However, in half of women treated with danazol, symptoms recur within a year. In these cases, treatment can be restarted.

Hereditary angiodema

Treatment for hereditary angioedema usually starts with a 200 mg dose given two or three times a day. Further adjustments are made based on the patient's response. If episodes are prevented, the amount may be decreased by half. If an attack occurs, the dose can be increased by up to 200 mg.

Other

Treatment of anemia in myelodysplastic syndrome usually begins with a dose of 200 mg three times a day.

Precautions

The use of danazol requires that liver and kidney function be routinely tested, as it can cause damage to these organs. In fact, with long-term use, there have been reported incidents of cancerous tumors in the liver.

Breast cancer should be ruled out prior to starting treatment. This may be difficult when there are multiple nodules in the breast. Any lumps that persist once danazol has started warrant consideration for breast cancer. Although danazol is effective in managing dysfunctional uterine bleeding, it should not be used in cases where **endometrial cancer** has not been ruled out.

Danazol should be used cautiously in people with high cholesterol. Danazol may cause a decrease in high-density lipoproteins (HDL; "good cholesterol"), which

KEY TERMS

Androgen—A steroid that produces masculine characteristics.

Cytopenia—Deficiencies of certain elements in blood, such as red blood cells, white blood cells and/or platelets.

Menorrhagia —Excessive menstrual bleeding.

in, high levels, remove cholesterol from the arteries. At the same time, danazol can cause an increase in the low density lipoproteins (LDL; ''bad cholesterol''), which act to move cholesterol into the arteries.

Danazol can cause androgenic effects on the fetus, and should not be used during pregnancy. Effects on a female fetus can include genital abnormalities such as clitoral enlargement, labia fusion, or vaginal closure. Treatment should not be initiated until pregnancy is ruled out. Throughout therapy, non-hormonal methods of birth control should be used to prevent pregnancy. If pregnancy does occur, the drug should be stopped and a doctor notified immediately.

Danazol is rarely associated with a condition called benign intracranial hypertension, symptoms of which include headache, nausea, vomiting, and visual disturbances. Should these symptoms occur, patients should stop taking the drug and see a neurologist.

When men, particularly adolescent men, take danazol, semen should be tested for volume, viscosity, sperm-count, and sperm motility every three to four months. Any changes may indicate a need to stop treatment.

Conditions that are worsened by swelling, a possible side effect of danazol, should be carefully monitored. This is particularly relevant in patients with epilepsy or cardiac problems.

Side effects

Long-term effects of danazol are unknown. Androgenic side effects may result, and may be an effect of decreased estrogen. These symptoms may include acne, swelling, abnormal hair growth, decreased breast size, deepening of voice, oily skin or hair, weight gain, enlargement of the clitoris, or reduction in the size of the testicles. Flushing, sweating, vaginitis, nervousness or emotional lability (instability) may also develop. Danazol may cause liver damage. In addition to routine lab testing, patients should be monitored for yellowing of the skin or whites of the eyes due to jaundice.

Interactions

The effects of oral anticoagulants, such as coumadin, may be increased in patients taking danazol, and should be used with caution. Individuals taking insulin for diabetes should carefully monitor their blood sugars. Taken in conjunction with danazol, insulin's effects are reduced. Danazol is also known to increase effects of the medications **carbamazepine** and cyclosporine.

Tamara Brown, R.N.

Daunorubicin

Definition

Daunorubicin is an anti-cancer drug that kills cancer cells. The brand names are DaunoXome for the liposomal formulation and Cerubidine for the daunorubicin hydrochloride formulation.

Purpose

Daunorubicin is available in two different formulations, the daunorubicin hydrochloride and daunorubicin citrate liposome. The liposomal daunorubicin formulation places the drug in lipid molecules. This formulation is able to penetrate cancer cells more effectively because of its smaller size, and it remains in the body longer when compared to the daunorubicin hydrochloride formulation. The daunorubicin hydrochloride is approved by the Food and Drug Administration (FDA) to treat **acute myelocytic leukemia** (AML) and **acute lymphocytic leukemia** (ALL). It is also sometimes used to treat chronic myelogenous leukemia (CML), non-Hodgkin's **lymphoma**, and psoriasis. The liposomal formulation of daunorubicin is used to treat advanced HIV-associated **Kaposi's sarcoma**.

Description

Daunorubicin interferes with the cells' production of DNA and RNA by inserting itself between the molecules that make up DNA and RNA. It also works by inhibiting the enzyme responsible for repairing of DNA (topoisomerase II enzyme). The structure of daunorubicin is very similar to that of **doxorubicin**, and both drugs function in the same way.

Recommended dosage

In the treatment of acute myelocytic leukemia (AML), the dose is 30 to 60 mg of daunorubicin per

square meter of body surface area given for three to five days, and the dose is repeated every three to four weeks.

In acute lymphocytic leukemia (ALL), 25 to 45 mg per square meter of body surface area of daunorubicin may be given on day one every week for four cycles, or alternatively may be given at a dose of 30 to 45 mg per square meter of body surface area for three days. The dose for patients receiving daunorubicin citrate liposome is 20 to 40 mg per square meter of body surface area every two weeks, or 100 mg per square meter of body surface area every three weeks.

Patients with decreased liver or kidney function may receive lower doses of the medication than other patients. This medication is usually administered directly into the vein (intravenous, or IV) over the course of three to five minutes. It may also be diluted in a solution to be given over fifteen minutes to one hour.

Precautions

A major problem with the use of daunorubicin is that it may cause a serious heart problem known as heart failure. Some authorities suggest that giving any individual patient more than 900 to 1000 mg of daunorubicin per square meter over the course of their entire life may increase risk of heart injury. Other authorities recommend that the total lifetime cumulative dose not exceed 550 milligrams per square meter. The patient's baseline heart function is obtained prior to starting therapy and is monitored every few cycles of **chemotherapy**. If the heart function is significantly decreased from baseline, the drug is discontinued.

Side effects

There is a risk that heart rhythm problems will occur during daunorubicin therapy. Later, patients may develop heart failure. However, patients receiving daunorubicin are, in fact, less likely to develop such problems than are patients receiving doxorubicin.

In addition, the activity of the bone marrow in producing white blood cells to fight infections, platelets to control bleeding, and red blood cells for oxygenation may be impaired by the drug. This and the development of heart problems are the major side effects that may cause doctors to lower the dose of daunorubicin.

Other side effects associated with daunorubicin therapy are nausea, vomiting, ulcerations of the mouth, **diarrhea**, and hair loss. In addition, the medication has a harmless side effect about which patients should be forewarned; urine and tears may take on a red color.

KEY TERMS

DNA—A molecule found in all living cells that contains tiny bits of genetic information

RNA—A molecule that interacts with the genetic information contained in cells.

Patients receiving daunorubicin in conjunction with certain other anticancer drugs may (very rarely) develop a certain type of leukemia. The drug is also an irritant to the skin and tissues of the body. Patients who notice burning or pain with infusion of the drug should notify the nurse immediately to assess if the drug has leaked from the vein into the surrounding tissue. If this occurs, the drug infusion is stopped immediately and appropriate actions are taken to minimize side effects due to tissue damage.

Bob Kirsch

D & C *see* **Dilatation and Curettage**

Demeclocycline

Definition

Demeclocycline, more accurately demeclocycline hydrochloride, is a broad-spectrum antibiotic of the tetracycline family. Demeclocycline is marketed under the trade name Declomycin.

Purpose

Demeclocycline is used to treat cancer patients who have developed a condition known as **syndrome of inappropriate antidiuretic hormone** (SIADH). A wide variety of malignacies, especially small-cell lung cancer, as well as various other non-cancer conditions, give rise to SIADH, which is caused by overproduction of antidiuretic hormone (ADH). SIADH can also develop as a side effect of the anticancer drugs **vincristine**, vinblastine, **cisplatin**, **melphalan**, and **cyclophosphamide**. The increased ADH levels lead to insufficient elimination of water from the kidneys, and the retained water leads to dilution of the serum sodium concentration, a condition called hyponatremia. Symptoms of hyponatremia include weight gain in spite of appetite loss, **fatigue**, headache, and confusion. When the condition is severe or the onset sudden, the symptoms may develop into seizures

or coma. Although treating the underlying cancer is the ideal approach, the metabolic imbalances may be alleviated in other ways. The tetracycline derivative demeclocycline has been found to be effective in treating SIADH.

Demeclocycline was originally approved by the Food and Drug Administration (FDA) to treat a wide variety of bacterial infections. It is thought that the tetracyclines work by preventing bacteria from synthesizing protein.

More recently, demeclocycline has been combined with hydrocortisone in a paste used by dentists to control inflammation and prevent infection in root canal and other endodontic procedures. The paste is sold under the trade name Ledermix.

Description

This tetracycline derivative is isolated from a mutant strain of the bacterium *Streptomyces aureofaciens*.

Demeclocycline was first investigated as a treatment for SIADH in 1976, and had become established as the treatment regimen of choice by 1986. The drug acts to interfere with the response of the kidneys to ADH and has consistently been found to be effective in treating SIADH with relatively few side effects.

Recommended dosage

Demeclocycline hydrochloride is taken orally. It is supplied as 150 and 300 mg tablets and 150 mg capsules. The usual dosage of demeclocycline for SIADH is from 600 to 1200 mg/day, and should not exceed 2400 mg/day. Within five days of beginning the drug, the diuretic action begins, and it generally lasts for two to six days after the drug is discontinued.

Precautions

Absorption of demeclocycline is reduced when taken with food or dairy products, and thus should be given one hour before or two hours after a meal or ingestion of dairy products. The dose should be taken with 8 oz (240 mL) of water, and the last dose of the day should be taken at least one hour before bedtime.

Antacids containing aluminum, calcium, or magnesium interfere with absorption of orally administered tetracyclines and should not used by patients taking demeclocycline.

Photosensitivity reactions are more frequent and more severe with demeclocycline than with other tetracyclines. Patients should be advised that this reaction can occur and be cautioned to avoid exposure to direct sunlight or ultraviolet light.

With renal impairment, even usual doses of demeclocycline may lead to accumulation of the drug and the possibility of liver toxicity. Serum level determinations of the drug may be advisable under such conditions, and the dosage should be lower than usual.

Tetracyclines can cross the placenta and can have toxic effects on the developing fetus, and the drug is found in the milk of lactating women taking tetracyclines. Tetracyclines form a complex with calcium and act to decrease the rate of bone growth in any bone-forming tissue while the drug is being administered.

Side effects

Dermatological

Skin reactions, including redness, swelling, rashes, and flaking or peeling of the skin can result from demeclocycline administration. Demeclocycline should be discontinued if the skin becomes swollen and reddened.

Patients taking demeclocycline are likely to be photosensitive. Phototoxic reactions occur with moderate to large doses and are characterized by severe skin burns resulting from direct exposure to sunlight.

Gastrointestinal

Demeclocycline can cause loss of appetite, nausea, vomiting, and **diarrhea**. Inflammations of the upper GI tract have also been reported as side effects, involving the tongue and esophagus, with resultant dysphagia, but many of these patients were found to have taken the medication immediately before going to bed. Inflammation of the small and large intestines has also been reported, and, as with all antibiotic therapy, overgrowth in the lower GI tract of other organisms, especially of the *candida* genus of yeast-like fungi, can lead to inflammatory lesions in the anogenital area.

Central nervous system

Dizziness, tinnitus, benign intracranial hypertension (pseudotumor cerebri), and visual disturbances have been reported. More rarely, myasthenic (Eaton-Lambert) syndrome and muscle weakness have been reported.

Immune system

Possible allergic reactions to demeclocycline include hives, angioedema, anaphylaxis, anaphylactoid purpura, pericarditis, and worsening of systemic lupus erythematosus.

Other

Superinfection due to overgrowth of nonsusceptible organisms is a common side effect of demeclocycline

KEY TERMS

Anaphylactoid purpura—A short-term allergic condition of blood vessels, found chiefly in children, that is characterized by wet sores on the skin of the buttocks, legs, and lower abdomen. Joint pain, stomach bleeding, and blood in the urine are also common findings. The disease, also called Henoch-Schonlein (Schonlein-Henoch) purpura, usually lasts for about 6 weeks and has no long-term effects unless kidney involvement is severe.

Anaphylaxis—A severe allergic reaction to a foreign substance (antigen) that a patient has had previous contact with, characterized by redness and swelling, itching, water build-up, and, in severe cases, extremely low blood pressure, lung spasms, and shock.

Angioedema—A sudden, painless, swelling of short duration that can affect the face, neck, lips, throat, hands, feet, genitals, or abdominal organs; also called angioneurotic edema.

Antidiuretic hormone—A peptide hormone, also called vasopressin, synthesized in the hypothalamus and released by the posterior pituitary gland in response to decreased blood volume, that stimulates capillary muscles and concentrates and reduces the elimination of urine.

Benign intracranial hypertension—Also called pseudotumor cerebri or meningeal hydrops, a condition of swelling of the optic nerve and mild paralysis of the cranial nerves, with headache, nausea, and vomiting.

Dysphagia—Difficulty in swallowing.

Hyponatremia—A condition in which the serum sodium concentration falls to less than 135 milliequivalents per liter (mEq/L), caused by too little excretion of water or by too much water in the bloodstream; in severe cases, hyponatremia leads to water intoxication, characterized by confusion, lethargy, muscle spasms, convulsions, and coma.

Lupus erythematosus—A long-term disease that affects women four times more often than men, characterized by severe swelling of the blood vessels giving rise to arthritis, kidney disorders, red rash over the nose and cheeks, weakness, fatigue, weight loss, photosensitivity, fever, and skin sores that may spread to the mucous membranes and other tissues of the body; also called systemic or disseminated lupus erythematosus.

Nephrogenic diabetes insipidus—A condition in which the kidneys do not retain urine, resulting in excess urination and thirst, and very watered-down urine.

Pancreatitis—An inflammation of the pancreas diagnosed on the basis of severe pain that begins in the abdomen and moves to the back, fever, loss of appetite, nausea, vomiting, and jaundice.

Pericarditis—An inflammation of the pericardium, the membrane covering the heart, marked by pain that begins in the chest and moves to the shoulder or neck, fever, difficulty breathing, and a dry cough.

Photosensitivity—An abnormal sensitivity of the skin to ultraviolet light, often resulting from use of an oral or topical drug, that leads to accelerated and severe burning and blistering of the skin.

Prothrombin—A plasma protein, produced by the liver and converted to thrombin by activation factors in the plasma, involved in blood coagulation; also called factor II.

Superinfection—An overgrowth, during antimicrobial treatment for another infection, of a microorganism not affected by the treatment.

Tetracycline—A broad-spectrum antibiotic.

Tinnitus—A sensation of ringing or other similar sound in the ears.

administration. Renal toxicity has been reported. Acute pancreatitis and nephrogenic diabetes insipidus are possible side effects of demeclocycline treatment. Increases in liver enzymes and hepatic toxicity have been rarely observed. Blood conditions such as **hemolytic anemia**, **thrombocytopenia**, **neutropenia**, and eosinophilia have also been reported. Individuals still undergoing tooth development (infants and children up to 8 years old, and in the fetus during the last half of pregnancy) may develop permanent yellowish-grayish-brown discoloration of the teeth and poor enamel development.

Interactions

Tetracyclines including demeclocycline can interfere with the bactericidal action of penicillins, and should not be administered together with penicillin. Tetracyclines coadministered with oral contraceptives

can render oral contraceptives less effective. The activity of plasma prothrombin can be depressed by tetracyclines, thus patients on anticoagulant therapy may be required to decrease their anticoagulant dosage.

Resources

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ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657-3000. <www.ashp.org>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

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Denileukin

Definition

Denileukin (denileukin difitox) is a fusion protein, or a protein made from two different proteins, that is used to treat recurrent **cutaneous T-cell lymphoma**.

Purpose

Cutaneous T-cell lymphoma (CTCL)is a form of non-Hodgkin's lymphoma, or an uncontrolled growth of cells in the lymph system that begins in the skin. It may spread to other organs.

Denileukin is known by the full name denileukin difitox, and also by the brand name Ontak. It causes the death of T cells or lymphocytes that are being made in enormous numbers by tricking the troublesome cells into binding with it, and then killing them.

Description

Denileukin is a genetically engineered protein, created by fusing a piece of the toxin that causes diphtheria with interleukin-2 (also known as IL-2 or **aldesleukin**). Because of the presence of IL-2 in the fusion protein denileukin, cells that have IL-2 receptors bind with it. Thus, the cells are fooled into binding with a protein they recognize, only to be killed by the toxin that is fused with it.

Not all malignant T cells and lymphocytes have IL-2 receptors. If the cells do not have the receptors, denileukin is not useful.

Recommended dosage

Denileukin is given through intravenous line. The best therapy course has not yet been determined. But the standard dose is either 9 or 18 micrograms per kilogram of body weight per day for five consecutive days, every three weeks.

Precautions

Because the use of the treatment can contribute to an environment that encourages infections, largely because of the fluid that accumulates around cells, patients must be monitored closely for infection.

Oncologists using the treatment must first test the cells of the patient for receptivity to IL-2. The treatment should not be used in patients who do not have the specific receptors for IL-2 that tricks the cells into binding with denileukin. The receptors of the cells that will bind all have a component known as CD25.

About 60% of patients diagnosed with CTCL have the receptors for IL-2. The Food and Drug Administration (FDA) has approved denileukin for use in patients who have not responded to other treatments.

Side effects

Vascular leak, or the seepage of fluid from blood vessels, accumulates and causes swelling (edema) and

KEY TERMS

Genetically engineered—An organism that has been modified by the intervention of humans, usually by the addition of DNA, or hereditary material, from one species to the DNA of another species.

Intravenous line—A tube that is inserted directly into a vein to carry medicine directly to the blood stream, bypassing the stomach and other digestive organs that might alter the medicine.

Kilogram—Metric measure that equals 2.2 pounds.

Lymphatic system—The system that collects and returns fluid in tissues to the blood vessels and produces defensive agents for fighting infection and invasion by foreign bodies.

Lymphocyte—One of the specialized white blood cells in the lymphatic system.

Microgram—One-thousandth of a milligram, and one-millionth of a gram.

Milligram—One-thousandth of a gram. There are one thousand grams in a kilogram. A gram is the metric measure that equals about 0.035 ounces.

Receptor—A part of a cell that is a structural and functional fit for a compound to which the cell is exposed.

Recurrent—Returns, or keeps coming back.

T cell—A cell in the lymphatic system that contributes to immunity by attacking foreign bodies, such as bacteria and viruses, directly.

may contribute to infection. Infection is an important and dangerous side effect. It causes some patients to discontinue treatment. Flu symptoms are common, and include pain, headache, and nausea and vomiting. Low blood pressure, skin eruptions, and liver toxicity (poisoning) are also side effects. Fast heart rate and numbness are possible side effects.

Interactions

Denileukin was so recently approved for use that drug interaction studies are not available. As with all drugs, the physician in charge of the care plan must be told about all drugs a patient is taking that might interfere with the activity of the denileukin.

Diane M. Calabrese

Depression

Description

Everybody feels sad sometimes, but to be clinically depressed is not just a matter of feeling sad. A patient with cancer is diagnosed as having major depression only if certain symptoms, such as loss of pleasure or thoughts of death, are present for at least two weeks. Only a healthcare professional can accurately determine whether a patient is depressed or is simply upset because of the disease.

A note on depression and children with cancer

Few children with cancer experience depression. For many children survivors of cancer, the experience of having had cancer makes them deeper, more understanding human beings later in adulthood and old age. However, some children with cancer do experience depression, sleep problems, and relationship problems. Depression appearing in a child who has cancer should be treated by a healthcare professional.

The symptoms of depression in children are somewhat different from those in adults. The physician should be notified of a sad mood (or, in children less than six years of age, a facial expression that appears to express sadness) that continues for at least two weeks and is accompanied by at least four of the following: (a) appetite changes, (b) sleep problems or excessive sleep, (c) excessive activity or inactivity, (d) loss of pleasure, (e) not caring about anything, (f) fatigue, (g) being overly critical of himself or herself, (h) feeling worthless or guilty for no apparent reason, (i) inability to concentrate, and (j) thoughts of death.

Are most people who have cancer depressed?

Most people who have cancer are not depressed. Depression is found in cancer patients about as frequently as in patients hospitalized for major, noncancer illnesses such as heart disease. However, depression is more often present in people who have cancer than in the general population. Approximately one out of eight people with cancer are depressed. Among hospitalized people with cancer, roughly one in four is depressed.

Depression and embarrassment

Doctors and nurses can do a great deal to help a depressed person feel better. Being embarrassed can get in the way of the patient's getting help. While depression is a disease that happens to a minority of cancer patients,

it does appear in a sizable number of these patients. Doctors and nurses are trained to deal with depression in cancer patients. If one out of eight people with cancer are depressed, it is no surprise to healthcare professionals that some patients require treatment for depression. It is not "bothering" a good health care professional to let them know that the patient is experiencing some symptoms that may signal depression. Competent doctors and nurses will not think less of a patient who is depressed. Rather, they will respect the patient who acknowledges the willingness to seek and accept treatment for depression. Cooperative patients are not those who hide depression but those who deal with depression when it appears. Dealing honestly and with the aid of doctors and allied healthcare professionals is the right way to address any cancer-related symptom.

How does depression affect someone who has cancer?

Depression is not something that can be pointed to, as one would point to a runny nose or an earache. That does not mean it is not real, nor does it mean the depression does not have a major effect on the cancer patient. The fact is that depression may not only affect what patients can do and how they feel, depression may also affect how well they function and how long they live.

A study of patients with **acute leukemia** who were receiving **bone marrow transplantation** found that those who were not depressed lived longer. A study of **breast cancer** patients showed that depression can be treated successfully and life extended. In this study, women with metastatic breast cancer who joined a support group lived twice as long as matched patients who did not join a support group. In light of these types of studies it would be incorrect to assume that depressed cancer patients who work with their doctors and nurses to treat their depression do not live as long as patients without depression.

Untreated depression or inadequately treated depression may slow recovery time. A study of depressed colorectal cancer patients found they were not able to function as well six months after surgery as patients who were not depressed. Another study found that breast cancer patients who were more anxious and depressed felt more pain than those who were not. Other studies have also shown that depression affects how people function and cope with illness.

Causes

It is certainly understandable that someone with a serious illness feels sad. Many cancer patients are confronted with difficulties. These may include having to take medications, dealing with the side effects of these medications, undergoing operations, submitting to other medical procedures, and generally taking time away from other things they would prefer to do. In addition, many patients feel a sense of loss. They may feel a loss of good health; there may be a loss of part of the body, such as a segment of a breast; there may be a loss of the ability to do certain tasks. There may also be financial strains. Any such things are difficult for most people to deal with. It takes time and effort, and sometimes medical intervention, for people to deal with such loss and gradually get their lives back on track.

If patients are in pain it is extremely important that the pain be adequately treated. Pain is often under-treated. When pain is not treated appropriately, patients may be more likely to develop depression.

Patients with cancer of the pancreas are particularly likely to become depressed. In addition, patients with breast, colon, gynecologic, oropharyngeal, and **stomach cancer** are more likely to experience depression than patients with other types of cancers. No one knows why depression is more likely to be associated with these cancers.

Approximately one out of every four patients with depression associated with cancer already was depressed at the time of diagnosis. In contrast, approximately three out of four develop the depression after the diagnosis has been made.

Risk factors for depression among cancer patients

Anyone can become depressed, and this includes people with cancer and people who are perfectly healthy. Often, there is no way of predicting who will develop major depression. However, some groups of cancer patients are more likely to develop depression than are others. This include patients who:

- are younger
- have a personal or family history of depression or other mental health problems
- have a personal or family history of substance abuse
- have **body image** problems
- are hospitalized
- are experiencing unrelieved cancer-related symptoms, such as pain
- have advanced or relapsed cancer, or have experienced a treatment failure
- have been diagnosed with stroke or with Parkinson's disease

In addition, some patients are receiving medicines that may cause depression as a side effect. Among these

medicines are certain anticancer drugs, antihistamines, blood pressure medicines, anti-Parkinson's disease medicines, medications for convulsions, sedatives, steroids, stimulants, and tranquilizers.

Signs and symptoms

A patient with cancer is diagnosed as having major depression only if certain symptoms are present for at least two weeks. Among these symptoms are:(a) loss of pleasure or interest in activities, (b) major **weight loss** or weight gain not associated with dieting, (c) serious sleep problems, (d) loss of energy, (e) **fatigue**, (f) feeling worthless, (g) feeling guilty without adequate reason, (h) problems concentrating, (i) indecisiveness, (j) thoughts of death or suicide. Symptoms such as sleep problems, fatigue, and weight loss may, however, affect cancer patients who are not depressed in the slightest. So, the diagnosis must be made by a healthcare professional.

Often depression appears gradually. At first, the patient seems no more than sad. At times, the person who is in a very early stage of depression brightens up. For many people things never get worse than this and true depression never touches them. However, other people progress to where negative thoughts have a grip upon them.

Gradually, some of the neurotransmitters in the nervous system may stop working in the most healthy way. Neurotransmitters are the chemicals released by nerves to communicate with other nerves. Once a patient's neurotransmitters are affected, the depression is definitely not simply happening in the patient's mind. The way the body uses actual chemicals is being altered by the depressive disease.

Precisely how the depression shows itself may differ from patient to patient. For example, some patients start to respond to little setbacks as though these are catastrophes. Other patients start making big assumptions, usually in negative directions; for example, they may assume their current therapy will not help them, even although there is good medical evidence that it probably will. For yet another example, they may blame themselves for having cancer, or irrationally see the cancer as a punishment visited upon them for something they have done. Patients may try to be too perfect and repeatedly fail. They may think other people have negative feelings about them, or they may focus upon the negative portions of situations. One danger is that the looming depression may encourage patients to push away and alienate those health professionals, friends, and family members who are trying to be helpful. For a final example, a depressed patient may deny the seriousness of the cancer, saying something like, "The tumor is small so I don't really need to be careful about taking my medicines."

Some patients experience a milder form of depression, called dysthymia. Symptoms of dysthymia include annoyance, feelings of sadness, irritability, loss of pleasure, and self-criticism. The patient with dysthymia may develop aches and pains, express excessive guilt, and distance themselves from loved ones. Dysthymia may be almost unnoticeable; however, many patients with dysthymia are unable to function quite as well as they can when they are healthy.

Depression screens

The attending doctor or nurse may request that the patient complete a depression screen. This screen is nothing more than a page or two of questions about how the patient is feeling. The patient's responses give healthcare professionals a picture of whether or not depression may be present.

Prevention

It is important for patients to have an idea of the psychological and social stressors they may have to address because of the cancer. Knowing in advance that something may be a problem is a good way of making sure that it is not quite as stressful once it does appear as it otherwise would be. Patients, their families, and close friends should be able to recognize the most important signs and symptoms of depression and should know which healthcare professional to call should depression appear. However, no one except a professional is capable of accurately diagnosing depression. It is a good idea to try to develop an honest relationship with a healthcare professional you trust. Parents of a child who has cancer may find a parent support group helpful, as there is a great deal to learn from other parents who have been through a similar situation.

Treatments

Most important is that study after study has shown that depression in cancer patients can be successfully treated. It is important to understand that this problem probably can get better. Several different approaches to treatment can be taken, and several of these approaches can be effectively combined with one another

If the patient has a doctor or nurse capable of providing sustained emotional support, that can be helpful. On the other hand, it is important for patients to realize that doctors and nurses are usually extremely busy and that it may be necessary to find someone else to provide sustained emotional support. This other person may be a

trained professional, such as a social worker, a psychiatric nurse, a psychologist, or a psychiatrist. The persons who provide support may also be family members or friends. A support group may be helpful. During periods of crisis, it is beneficial to have several people who can provide support. The family member or friend who is trying to provide such support should try to listen well and sympathetically.

Cognitive interventions

Cognitive interventions are also known as cognitive-behavioral treatment (CBT). CBT helps patients' view in a realistic way what is happening to them, where they are, and what they should or should not be doing. This type of intervention can be useful in helping patients give up negative perspectives and replace them with views that rely more upon the facts about what is going on. CBT may be practiced with a healthcare provider, or in a group with other patients and one or more providers.

Among the techniques CBT makes use of are:

- Cognitive distraction: This is the phrase used for techniques that shift the mind-frame of the patient from negative things to more positive thoughts. Music is one of the basic tools of cognitive distraction. Patients should be encouraged to listen to the type of music they like best. Headphones may be helpful if brought to diagnostic and treatment sessions and occasions when waiting is necessary. Imagery is another technique important for cognitive distraction. Imagery can help the mind shift from negative thoughts and difficult situations to helpful images. Each patient should select those images that feel right and good. For one patient this may be swimming at the beach; for another, visiting special friends; for another, walking through the forest.
- Psychoeducation: This CBT technique involves providing information to patients so patients can feel that what is going on is not entirely beyond their control. People often find it difficult to deal with the unknown, and psychoeducation attempts to remove some of what is unknown. Another important psychoeducation technique is having patients make lists of questions to ask their nurse or doctor.
- Image rehearsal: This CBT technique involves working with a healthcare professional. The patient may use image rehearsal to rehearse some activity she or he finds to be stressful. For example, image rehearsal may be used if the patient finds MRI scans or radiation treatments to be stressful.

Other CBT techniques involve relaxation techniques and the conscious decision to participate in activities the patient likes doing.

Psychotherapy

Talking to a psychologist, social worker, psychiatric nurse, psychiatrist, or other health care professional can be helpful. In addition to the cancer and problems associated with therapy, this talk therapy can help the patient address unresolved matters that were already bothersome before cancer was diagnosed.

Group therapy

Studies have shown group therapy to be an effective approach for patients with cancer-related depression. Various approaches to group therapy may be taken. In all, however, it involves communication not only between patient and healthcare professional, but also among and between patients. Group therapy can also be helpful for loved ones of cancer patients.

Important to note is that studies have shown that cancer patients may tend to isolate themselves from friends and family. In other words, the amount of contact and communication between friends and family may be less than it had been before cancer was diagnosed. This is not a helpful trend. Research suggests that social support can have beneficial effects on a person's physical health. Group therapy can provide this type of social support to patients. In addition, group therapy may furnish a place where patients are able to learn about how to maintain contact with family and friends. It can also provide a way for patients to identify which family members and friends are not supportive.

Medication

A variety of antidepressant medications are available. Among those most frequently prescribed are psychostimulants, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs). These medications help return the neurotransmitters to a normal, balanced function. There are at least three different psychostimulants, six different TCAs, three different SSRIs, and three different MAOIs that doctors may choose among. In addition, there are various other medications that have proven to be effective as treatment for depression. All of these drugs have been shown to work well in general; however, while one specific type of drug may be appropriate for one patient, another patient may require a completely different type of drug. Use of some of these drugs may be accompanied by side effects. Just as there are different antidepressant drugs, so are there different side effects that may appear. However, many patients have no side effects from antidepressant medications or, at most, exhibit

KEY TERMS

Cognitive-behavioral therapy—One of several effective ways of treating depression in cancer patients. CBT helps patients view what is happening to them in a realistic way. It may make use of music, imagery, and providing accurate information.

Depression screen—A questionnaire on how the patient is feeling used to help healthcare professionals diagnose depression.

Dysthymia—A milder form of depression.

only minor side effects. Other patients find that, although they had side effects from one drug, they experienced no side effects after they switched to another medication. Many patients find they are able to successfully combine medications and other treatment approaches, but honest communication with the physician is essestial.

The suicidal patient

If a patient is suicidal it is extremely important to immediately contact a healthcare professional capable of dealing with such a crisis.

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Bob Kirsch

Dexamethasone

Definition

Dexamethasone is a synthetic glucocorticoid. Its naturally occuring counterparts are hydrocortisone and cortisone. Although the drug is used in a variety of ways, in general, it reduces inflammation and depresses the immune system. Dexamethasone may also be called by its brand name, Decadron.

Purpose

Dexamethasone is used in the treatment of many disorders. For example, it may be used:

- as replacement therapy in the treatment of Addison's disease
- in the management of various inflammatory disorders, such as rheumatoid arthritis
- to coat drug-eluting stents, which are devices used in treating coronary artery disease to reduce the chance that previously clogged arteries will become blocked again
- in managing such allergic disorders as asthma
- as induction therapy prior to stem cell transplantation

Patients with ulcerative colitis may benefit from dexamethasone therapy, as might those with exacerbations of multiple sclerosis. Such blood disorders as thrombocytopenic purpura or erythroblastopenia, may also be managed with dexamethasone.

Dexamethasone is often prescribed to patients with cancer. In some cases, the drug is part of the drug treatment for the disease, and in other cases it is used to manage side effects caused by the treatment or the cancer itself. For example, dexamethasone may be given to treat nausea and vomiting associated with chemotherapy.

Dexamethasone may be used to decrease abnormally high levels of potassium that develop in association with cancer. In some cases, it may be used as palliation in leukemia or **lymphoma**. Because of its antiinflammatory properties, dexamethasone may help reduce swelling in the brain caused by a brain tumor. It may also help prevent hypersensitivity reactions associated with drugs like **paclitaxel**. Dexamethasone is also commonly used to treat nausea associated with **chemotherapy**. It is particularly useful with the drug **cisplatin**, which frequently causes **nausea and vomiting**.

In non-Hodgkin's lymphoma (NHL), dexamethasone is part of a drug regimen known as DHAP. Here, dexamethasone is given with chemotherapy drugs called cisplatin and **cytarabine**. Also in treating NHL,

dexamethasone may be used in a regimen caled ''m-BACOD,'' which also includes the administration of **methotrexate**, **leucovorin**, **bleomycin**, **doxorubicin**, **cyclophosphamide**, and **vincristine**. Dexamethasone may also be helpful in patients with **multiple myeloma**. In the EDAP regimen, dexamethasone is given with **etoposide**, cytosine arabinoside (cytarabine), and cisplatin; in VAD, it is given with vincristine and doxorubicin.

Description

Patients should not stop taking dexamethasone without first consulting their physician. When dexamethasone treatment stops, it must be gradually reduced over time before it can be completely discontinued. Sudden withdrawal of glucocorticoids may result in adrenal insufficiency.

When possible, the drug should be taken before nine A.M. to imitate the time that the body's corticosteroid levels are typically at their highest. A child taking dexamethasone will be carefully monitored to ensure the drug is not affecting his or her growth. Patients taking large doses of dexamethasone should try to take the drug with meals. Antacids may be recommended between meals to reduce gastrointestinal effects and to prevent peptic ulcer.

Recommended dosage

Dexamethasone is available in oral, intravenous (IV), topical, ophthalmic, or inhaled form. In cancer patients, the oral and IV routes are used most frequently. The pill is available in several color-coded dosages [0.25 milligrams (mg), 0.5mg, 0.75mg, 1.5mg, 4mg, and 6mg]. Dexamethasone should be given very slowly by the IV route.

Dosages to treat disease are highly individualized, but generally start at 0.75 to 9.0 mg per day. The lowest therapeutic dose should be given, though amounts given may need to be increased during times of stress. Dosages of medications may be changed based on factors specific to the individual. The following dosages are general guidelines for dexamethasone when it is used in conjunction with chemotherapy agents:

- DHAP. Forty milligrams of dexamethasone is given in pill or IV form per day for the first four days of treatment, followed by cisplatin and cytarabine.
- M-BACOD. Six milligrams per meter square (mg/m2) of dexamethasone is given as a pill on the first five days of treatment.
- EDAP. Forty milligrams of dexamethasone is given in pill form on the first four days of treatment. It is given again on days 9-12, and 17-20.

When used to prevent or manage nausea or vomiting associated with chemotherapy, dexamethasone is given in the following dosages: 4–20 mg IV every 4–6 hours. Alternatively, a one-time dose of 10–20 mg may be given IV. When pills are preferred, 4–8 mg of dexamethasone may be given four times, every four hours. When used to prevent hypersensitivity reactions in paclitaxel treatment, 20mg should be given orally twelve and six hours before treatment begins.

Precautions

Dexamethasone should be used cautiously in patients with kidney or liver problems, hypothyroidism, high blood pressure, or a history of heart attack. Patients with diabetes mellitus should monitor blood sugar levels carefully, as hyperglycemia may result. If changes occur, patients should notify their doctors immediately. Sudden cessation of dexamethasone therapy is dangerous for patients on therapy for longer than two weeks. The drug should be gradually withdrawn under a physician's guidance.

Side effects

Adverse effects vary widely, and depend on the dosage and route of the drug. Certain drugs may result in decreased blood levels, and therefore render dexamethasone less effective. Patients taking the following drugs should be carefully monitored for decreased levels of dexamethasone: **phenytoin**, phenobarbitol, ephedrine, and rifampin. Conversely, some drugs, such as troleandomycin, may increase blood levels of dexamethasone.

Because of its immunosuppressive properties, dexamethasone may decrease the signs and symptoms of infection. Depending on the amount of drug being administered, patients may consider taking measure to prevent infection by avoiding crowded areas and washing their hands frequently. Patients should inform their doctor if they notice a **fever**, sore throat, or cuts or abrasions that don't heal. Laboratory tests may also be affected—false negative results may occur in the nitroblu-tetrazolium test for bacterial infections.

Glucocorticoids, such as hydrocortisone, tend to make the body retain salt. Although dexamethasone's salt-retaining properties are not as severe as hydrocortisone's, salt retention may result in fluid and electrolyte imbalances. Patients at risk may experience high blood pressure or even congestive heart failure. Weight gain or swelling may indicate salt and fluid retention.

Other adverse effects may include headache, dizziness, insomnia, increased appetite, mood swings, menstrual changes, muscle weakness, acne and/or sweating. **Depression** may be worsened with dexamethasone use.

KEY TERMS

Addison's disease—A potentially life-threatening condition that results when adrenocortical function fails. Hypoadrenalism.

Elute—In chemistry, to remove by dissolving or washing. A drug-eluting stent is one that contains a medication to reduce inflammation.

Glucocorticoid—An adrenocortical steroid hormone that is stimulated by the anterior pituitary. The three naturally occuring types are hydrocortisone, corticosterone, and cortisone.

Hyperglycemia—An abnormally increased level of glucose (sugar) in the blood.

Induction therapy—Chemotherapy that is given as the initial treatment for cancer, prior to surgery or transplantation.

Palliation—Therapy aimed at relieving symptoms and promoting comfort, but not producing a cure.

Stent—A small tube inserted surgically into an artery to hold it open. Stents may be coated with dexamethasone to reduce inflammation within the blood vessel.

Some men experience changes in the motility and number of their sperm with steroid treatment. Patients should talk to their doctors about any unusual symptoms they experience. In cancer patients, increased appetite may actually be beneficial.

Dexamethasone crosses the placenta and is excreted in breast milk. If a pregnant woman is taking large doses of the drug, her newborn should be monitored for evidence of hypoadrenalism. Optimally, breast-feeding should be avoided. There is some concern that dexamethasone, in large quantities, suppresses growth or disrupts the baby's normal corticosteroid production.

Interactions

Patients should discuss all their medications, prescription and non-prescription, with their doctor. If dexamethasone is administered in amounts that suppress the immune system, live **vaccines**, such as small pox, should not be administered. Dexamethasone may alter the effect of anticoagulant drugs. Frequent laboratory tests should be performed to monitor blood levels. If dexamethasone is given with diuretics, potassium levels may be abnormally low, and should be frequently monotired. Doctors may recommend that patients on long-term therapy follow a potassium-rich diet.

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American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657-3000. <www.ashp.org>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

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Dexrazoxane

Definition

Dexrazoxane, known by the brand name Zinecard or may be referred to as ADR-529, is a medicine that protects the heart from damage caused by the **chemotherapy** drug **doxorubicin**.

Purpose

Dexrazoxane is approved by the Food and Drug Administration (FDA) as a protectant medicine given to women with metastatic **breast cancer** who are being treated with the chemotherapy drug doxorubicin. In most cases these women already will have received greater than 300 mg per square meter (mg/m^2) of the chemotherapy drug doxorubicin before dexrazoxane is added. Dexrazoxane is given in combination with doxorubicin. Doxorubicin can cause damage to heart muscle and the risk of this damage increases as the total dose increases. The addition of dexrazoxane at the appropriate time in

therapy can decrease the extent of damage to the heart muscle.

Description

Dexrazoxane is a clear, colorless solution. It is administered intravenously, into a vein, over a 15-30 minute period. Dexrazoxane is given within 30 minutes prior to receiving the doxorubicin. When doxorubicin gets into cells, it combines with iron to form toxic substances that destroy heart muscle. Dexrazoxane interferes with the doxorubicin binding to the iron compound so that the toxic substance is not formed and the heart muscle is protected.

Recommended dosage

Dexrazoxane doses can be determined using a mathematical calculation that measures a person's body surface area (BSA). This number is dependent upon a patient's height and weight. The larger the person, the greater the body surface area. Body surface area is measured in units known as meters squared (m^2). The body surface area is calculated and then multiplied by the drug dosage in mg/m^2. This calculates the actual dose a patient is to receive.

Dexrazoxane is dosed in mg/m^2 as a 10:1 ratio of the doxorubicin dose. For example, if a patient is to receive doxorubicin 50 mg/m^2, then the patient would receive dexrazoxane 500 mg/m^2. Once the dose is determined, the drug is administered either directly into the vein over a few minutes as an intravenous push, or as a quick infusion from an infusion bag. This is then followed by the doxorubicin intravenously.

Precautions

Blood counts will be monitored regularly while on dexrazoxane therapy. During a certain time period after receiving chemotherapy, there is an increased risk of getting infections. Caution should be taken to avoid unnecessary exposure to crowds and people with infections.

Patients should not expect their doctor to use dexrazoxane the first time they receive chemotherapy. It is thought that dexrazoxane may interfere with the chemotherapy drug's ability to destroy cancer cells. Dexrazoxane is therefore only used when absolutely necessary.

Patients who may be pregnant or are trying to become pregnant should tell their doctor before receiving dexrazoxane.

Chemotherapy can cause men and women to be sterile (not able to have children). It is unknown if dexrazoxane causes sterility.

KEY TERMS

Anemia—A lower than normal red blood cell count.

Anthracyclines—a group of chemotherapy medicines that are used to treat cancer. They have similar characteristics and are known for their ability to cause heart damage. The drugs included as anthracyclines are doxorubicin, daunorubicin, idarubicin, and epirubicin.

Antineoplastics—Medicines used to treat cancers.

Chemotherapy—A specific drug used to treat cancer.

Food and Drug Administration—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives approval to pharmaceutical companies for commercial marketing of their products

Intravenous—To enter the body through a vein.

Metastatic—Cancer that has spread to one or more parts of the body.

Neutropenia—A lower than normal white blood cell count.

Radiation therapy—The use of high-energy beams focused to treat cancerous tumors.

Sterility—Inability to have children.

Toxic—Poisonous.

Patients should check with their doctors before receiving live virus **vaccines** while on chemotherapy along with dexrazoxane.

Side effects

The most common side effect from receiving the dexrazoxane is pain at the injection site. Another common side effect when dexrazoxane is given with chemotherapy is that the blood counts fall lower than with just chemotherapy alone. However, the time it takes for the blood counts to return to normal is the same with or without the dexrazoxane.

Low blood counts, referred to as **myelosuppression**, are expected due to chemotherapy with dexrazoxane administration. A low white blood cell count is called **neutropenia**, and patients are at an increased risk of developing a **fever** and infections. Platelets are blood cells in the body that allow for the formation of clots. When the platelet count is low, patients are at an increased risk for bruising and bleeding. Low red blood

cell counts, referred to as **anemia**, may also occur due to chemotherapy administration. Low red counts cause **fatigue**.

Most other side effects occur due to the administration of the chemotherapy agents that accompany dexrazoxane. Common side effects include **nausea and vomiting**. Patients are given medicines before receiving chemotherapy that can help prevent or decrease these side effects from happening. Other common side effects are hair loss (alopecia), fatigue, loss of appetite, mouth sores, fevers, infections, **diarrhea**, and changes in liver function.

Less common side effects are nerve damage, swelling and inflammation of the veins where the chemotherapy is administered, difficulty swallowing, bleeding, **itching**, and skin reactions in areas of previous radiation.

All side effects a patient experiences should be reported to his or her doctor.

Interactions

Dexrazoxane should only be used with chemotherapy combinations that contain doxorubicin or other agents in the anthracycline class of antineoplastics.

Patients should tell their doctors if they have a known allergic reaction to dexrazoxane or any other medications or substances, such as foods and preservatives. Before taking any new medications, including nonprescription medications, **vitamins**, and herbal medications, the patients should notify their doctors.

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Diarrhea

Description

Diarrhea is the abnormal increase of liquid in stool and increase in the frequency of passing stool (defecation). The person with diarrhea has watery or loose stool more than three times a day. Other symptoms include cramping, pain, feeling the urge to defecate, irritation of the skin around the anus (perianal), and inability to control defecation (fecal **incontinence**). Approximately 10% of the patients with advanced cancer suffer from diarrhea. Diarrhea lasting fewer than two weeks is called "acute diarrhea," and diarrhea lasting for longer than two months is called "chronic diarrhea."

Diarrhea is a debilitating condition that can significantly affect quality of life. Diarrhea can prevent patients from participating in social activities and going to work. Persons with diarrhea fear soiling their clothing or bed linens, a fear that prevents them from leaving home. Loss of sleep due to nighttime diarrhea can cause fatigue, which ultimately affects the patient's ability to function normally. Uncontrolled diarrhea can lead to chemical imbalances, loss of fluids (dehydration), and even death.

Causes

Although there are many causes of diarrhea, only those associated with cancer will be discussed. The most common cause of diarrhea in cancer patients is related to constipation or its treatment. Cancer patients may experience diarrhea as a result of their treatment, or it can be due to dietary changes, infections, hormone imbalances, digestion disorders, or inflammation. Treatment-related diarrhea can be caused by **chemotherapy**, hormone therapy, **radiation therapy**, biological response modifiers (drugs that improve the patient's immune system), or surgery. In addition, cancer patients may develop temporary lactose intolerance, which causes diarrhea.

Chemotherapy drugs kill the rapidly growing cancer cells. However, certain normal cells of the body are rapidly growing and they too are affected. Rapidly growing cells are found in the intestines, as well as other parts of the body. Diarrhea occurs as a result of injury to the cells of the intestine. These effects are temporary. Chemotherapy drugs, hormones, and biological response modifiers that frequently cause diarrhea include:

- Dactinomycin
- Daunorubicin
- Diethylstilbestrol diphosphate
- Doxorubicin
- Fluorouracil
- Flutamide
- Hydroxyurea
- Interferon
- Interleukin-2 (aldesleukin)
- **Irinotecan**
- Methotrexate
- Nitrosoureas
- Thioguanine

Radiation therapy can cause diarrhea if the intestines are in the treatment field. Diarrhea results from the injury and destruction of the cells lining the intestines, which leads to a decrease in the uptake (absorption) of fluids and an increase in the speed with which stool moves through the intestines. Radiation therapy can cause

diarrhea, and other intestinal problems, many months or years after treatment has been completed.

Diarrhea usually develops within one week following pretreatment (chemotherapy and irradiation) for **bone marrow transplantation**. This diarrhea usually disappears within two weeks. Also, bone marrow transplant patients with graft-versus-host disease develop severe diarrhea.

Treatments

Prevention

There are some measures that can prevent diarrhea. Patients who are receiving abdominal radiation therapy can be put into certain positions to minimize exposure of healthy intestines to radiation. Diarrhea caused by chemotherapy cannot be prevented; however, the administration of atropine during treatment with irinotecan may prevent diarrhea. Patients should stop taking dietary supplements, as these can cause diarrhea.

There are many dietary changes that can be made to prevent or reduce diarrhea. Foods to avoid include:

- whole grain breads and cereals
- fresh or frozen fruits (except banana)
- dried fruits
- fruit juices with pulp and prune juice
- raw vegetables
- canned onions, corn, olives, pickles, and Brussels sprouts
- fatty foods
- dried beans
- rich desserts
- milk and milk products
- alcohol and caffeinated coffee and tea
- spicy foods
- fried foods

Management

Of the utmost importance in the treatment of diarrhea is the replacement of fluids lost by frequent, watery stools. The patient should drink six to eight glasses of fluid daily, including clear broth, ginger ale (without the fizz), water, weak tea, and commercial formulas that contain sugars and minerals (electrolytes). Patients with severe diarrhea may need intravenous fluid replacement either at home or in the hospital.

Diarrhea can cause the perianal skin to become irritated and painful; therefore, it needs to be cleaned thoroughly after each bout of diarrhea. Baby wipes or a mild soap with water can be used to clean the irritated skin. The area should be patted dry and occasionally exposed to air. Taking a sitz bath (sitting in a bathtub of shallow water) with lukewarm water may relieve the discomfort. Petroleum jelly or other type of barrier cream may be used.

The patient should eat small, frequent meals. Foods and drinks should be taken at room temperature. Foods that can help control diarrhea include:

- bananas
- applesauce
- boiled white rice
- tapioca
- white bread
- plain pasta
- creamed cereals
- eggs
- potatoes (without skin; mashed or baked)
- fish
- chicken or turkey (without skin)

There are some medications that can slow down the movement of stool through the intestines and increase intestinal water absorption. The patient may need a combination of drugs and/or dose adjustments to achieve relief. A physician should be consulted before any over-the-counter antidiarrheal medications are taken. Antidiarrheal medications include:

- Atropine sulfate with diphenoxylate HCl (Lomotil)
- Codeine phosphate
- Loperimide HCl (Imodium-AD)
- Octreotide phosphate (Sandostatin)

These medications should not be used if infection as the cause of diarrhea has not been eliminated.

KEY TERMS

Defecation—The passage of stool from the body.

Dehydration—The condition caused by excessive loss of water from the body.

Electrolytes—Molecules, such as sodium and potassium, that are necessary for normal body functioning. Diarrhea can cause electrolytes to become lost and/or unbalanced.

Perianal—The skin surrounding the anal opening.

Patients who are experiencing diarrhea due to graft-versus-host disease will continue to take their immunosuppressant drugs. They may also be treated with **corticosteroids** and antidiarrheal medications.

Alternative and complementary therapies

Peppermint tea, chamomile tea, valerian capsules, or aloe vera juice may reduce cramping and intestinal spasms. An Ayurvedic physician may recommend taking equal parts of yogurt and water with fresh ginger, or a powder of beleric myrobalan fruit. Ginger capsules may relieve intestinal spasms and pain. Glutamine supplements may speed up the healing process and relieve irritated intestines.

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Belinda Rowland, Ph.D.

Diethylstilbestrol diphosphate

Definition

Diethylstilbestrol diphosphate is a synthetic (manufactured) form of the female hormone estrogen. Brand names for diethylstilbestrol include Stilphostrol, and is also referred to as Stilbestrol and DES.

Purpose

Diethylstilbestrol is used to relieve symptoms of advanced **breast cancer** that has metastasized, or spread, from the breast to other parts of the body. It is used to treat breast cancer in men and in postmenopausal women. Diethylstilbestrol also has been used to relieve symptoms of advanced cancer of the prostate in men.

Description

Diethylstilbestrol was the first form of estrogen made in the laboratory. It was prescribed to millions of women in the 1950s and 1960s to prevent miscarriage and premature birth. This use was discontinued in the 1970s, when abnormalities of the reproductive systems were found in some children of women who took the drug during pregnancy. Furthermore, daughters of women who took this drug during pregnancy are at an increased risk for developing certain types of cervical and vaginal cancers.

Diethylstilbestrol is used to relieve some symptoms of advanced breast cancer in certain men and women. The drug can interfere with the spread of cancer cells that require estrogen to grow and divide.

Diethylstilbestrol sometimes is used to relieve symptoms of advanced **prostate cancer** in men. This drug can lower the levels of the male hormone **testosterone**, which is required for the growth and division of these cancer cells. However, diethylstilbestrol can cause severe side effects in men, including breast enlargement and increased risk of heart disease and blood clots. Thus, it is no longer widely used for the treatment of prostate cancer.

Recommended dosage

Diethylstilbestrol usually is given as a pill, which should be taken at the same time each day. The dosage varies depending on body weight and the type of cancer that is being treated. For breast cancer, the dose is 15 mg per day.

For inoperable prostate cancer, the dose is 50 mg three times a day and can be increased up to 200 mg or more three times a day. Maximum dose is 1 gram a day. For the treatment of prostate cancer, diethylstilbestrol can also be injected slowly into a vein. The dosage may be as high as 1 gram per day for five or more days. The dosage then may be lowered to 250-500 mg once or twice per week.

Precautions

Diethylstilbestrol can cause serious birth defects in humans. Children of women who take diethylstilbestrol (DES) during pregnancy may develop reproductive system abnormalities at puberty, and daughters are at an increased risk for developing **vaginal cancer**. Therefore, this drug should not be taken by pregnant women, or by either the man or the woman at the time of conception. Women should not breast-feed infants while taking this drug, since estrogens pass into the breast milk.

Diethylstilbestrol may not be indicated, or should be used with caution, for individuals whose medical histories include any of the following:

- heart, kidney, or liver damage
- disease of the gallbladder or gallstones
- inflammation of the pancreas
- bone or uterine cancer
- fibroid tumors of the uterus
- unusual vaginal bleeding
- endometriosis (uterine cells in the ovaries or other pelvic organs)
- high cholesterol
- blood clots or circulatory problems in males

Side effects

Diethylstilbestrol affects normal cells as well as cancer cells, so side effects can occur with this medicine. The side effects associated with diethylstilbestrol usually are mild and temporary. Common side effects include:

- enlargement of the breasts
- breast tenderness
- decreased sexual desire
- voice changes
- swelling of the feet and lower legs
- fluid retention
- weight gain

Less common side effects of diethylstilbestrol include:

- nausea and vomiting during the first few weeks of treatment
- changes in vaginal bleeding
- loss of bladder control
- lumps or discharge from the breasts
- stomach, side, or abdominal pain
- yellow skin or eyesTaking the medicine with food may reduce or prevent nausea.

Rarely, diethylstilbestrol results in the formation of blood clots in the legs or in the lungs. This primarily affects men who are receiving high-dosage treatment for breast or prostate cancers. Symptoms of blood clots include:

- pain, redness, or swelling in the calf
- weakness or tingling in an arm or leg
- faintness
- sudden severe headache
- vision changes
- shortness of breath
- chest pain
- coughing up blood (hemoptysis)

Interactions

Medicines that may adversely affect the liver when taken along with diethylstilbestrol include:

- acetaminophen (as in Tylenol; long-term or high-dose usage)
- amiodarone (Cordarone)
- anabolic steroids (such as nandrolone, oxandrolone, oxymetholone, stanozolol)
- androgens (male hormones)
- antithyroid drugs that are used to treat an overactive thyroid
- birth control pills containing estrogen
- carbamazepine (Tegretol)
- carmustine (BiCNU)
- chloroquine (Aralen)
- dantrolene (Dantrium)
- daunorubicin (Cerubidine)
- disulfiram (Antabuse)
- divalproex (Depakote)
- etretinate (Tegison)
- gold salts to treat arthritis
- hydroxychloroquine (Plaquenil)
- isoniazid
- medicines to treat infections
- mercaptopurine (Purinethol)
- methotrexate (Mexate)
- methyldopa (Aldomet)

KEY TERMS

Estrogen—Female sex hormone.

Hormone—Substance produced by the body to regulate the activity of a tissue or organ.

Metastasis—Spread of cancer from its point of origin to other parts of the body.

Prostate—Gland in males that surrounds the urine tube (urethra) at the base of the bladder.

Testosterone—Principal male sex hormone.

- naltrexone (Trexan; long-term or high-dose usage))
- phenothiazines
- phenytoin (Dilantin)
- plicamycin (Mithracin)
- valproic acid (Depakene)In addition, diethylstilbestrol and other estrogens can prevent cyclosporine (Sandimmune) from being removed from the body, leading to possible kidney or liver problems. Protease inhibitors such as ritonavir (Norvir) may reduce the activity of diethylstilbestrol.

Margaret Alic, Ph.D.

Digital rectal examination

Definition

The digital rectal examination (DRE) is a routine part of the physical examination and includes manual examination of the rectum, anus and, in men, the prostate.

Purpose

The purpose of the digital rectal examination is to identify lesions within the rectum and the prostate. It is the most widely used and oldest technique for the detection of **prostate cancer** and is used in screening for **colon cancer** and for the detection of rectal polyps.

Description

Usually the patient is positioned on the left side with the knees close to the chest. Sometimes the patient is asked to stand up and lean over the examination table. For women, sometimes this examination is part of the routine gynecological exam, and it may be done in a different manner than described here.

During the examination, the health care practitioner examines the anus and the surrounding skin for hemorrhoids, tags, fissures and abscesses. After lubricating the gloved finger and anus, the examiner gently slides the finger into the anus and follows the contours of the rectum. The examiner notes the tone of the anus and feels the walls and the edges for texture, tenderness and masses as far as the examining finger can reach. The examiner evaluates the prostate for nodules and tenderness. Stool on the finger should be examined for blood, color, texture and tested for fecal occult blood.

The examination takes less than two minutes and can be uncomfortable when the patient is not relaxed or is anxious. Occasionally, when the DRE is performed on a man the penis may become erect. A gentle reminder and reassurance helps to relieve the embarrassment associated with the unexpected erection.

Preparation

The patient must be carefully positioned and the doctor should take care to explain the examination to the patient and to explain to the patient what to expect. The digital rectal examination may be uncomfortable and embarrassing. Much of the discomfort can be reduced by an understanding, unhurried and gentle examiner.

Precautions

When there are infections of the anus and of the rectum, the digital rectal examination should not be performed. Manipulation of the anal and rectal tissues increases the risk of infection and of bleeding.

Results

In the normal anus and rectum, there are no hemorrhoids or bleeding about the anus. The anal tone is not loose. The rectum is smooth and non-tender. No masses should be palpated, or felt.

The digital rectal examination is helpful in identifying areas of peritonitis or tender areas that can be felt through the wall of the rectum. It is used to identify perineal disease or deformity, abnormal location of the anus, rectal prolapse and atrophy of the gluteal muscle. Digital examination can detect a stenosis (or narrowing) of the anal canal, assess the tone and strength of the anal muscles or detect the presence of a rectal mass or fecal impaction.

Any masses, including hard stool, blood or tenderness is considered abnormal. Cancer masses may be flattened, nodular, cauliflower-like or ring-shaped. Polyps

KEY TERMS

Fissure—Any cleft or groove, normal or otherwise, especially a deep fold in the anus.

Lesion—Any pathological or traumatic discontinuity of tissues or loss of function of a part.

Palpation—A simple technique in which a doctor presses lightly on the surface of the body to feel the organs or tissues underneath.

Peritonitis—Inflammation of the peritoneum. It may be accompanied by abdominal pain and tenderness, constipation, vomiting and moderate fever.

Polyp—Growth, usually benign, protruding from a mucous membrane.

Rectal prolapse—Protrusion of the rectal mucous membrane through the anus.

Skin tag—A small outgrowth of skin tissue that may be smooth or irregular, flesh-colored and benign.

can be felt, but must be visualized using **anoscopy** or flexible **sigmoidoscopy** to be distinguished from other lesions, such as internal hemorrhoids or malignant growths. Hard masses of feces may be felt and may be removed.

Aftercare

Aftercare of the digital rectal examination is minimal. It requires removal of the lubricating jelly residue from around the anus. The lubricating jelly dissolves easily in water and may be washed off in bathing after the examination. It can be removed with toilet paper immediately after the examination.

See also Rectal cancer.

Resources

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Cheryl L. Branche, M. D.

DiGuglielmo syndrome

see **Acute erythroblastic leukemia**

Dilatation and curettage

Definition

Dilatation and curettage (D&C) is a gynecological procedure in which the lining of the uterus (endometrium) is scraped away.

Purpose

D&C is commonly used to obtain tissue for microscopic evaluation to rule out cancer. The procedure may also be used to diagnose and treat heavy menstrual bleeding and to diagnose endometrial polyps and uterine fibroids. D&C can be used to remove pregnancy tissue after a miscarriage, incomplete abortion, or childbirth, or as an early abortion technique up to 16 weeks. Endometrial polyps may be removed, and sometimes benign uterine tumors (fibroids) may be scraped away.

Description

D&C is usually performed under general anesthesia, although local or epidural anesthesia can also be used. Using local anesthesia reduces risk and costs, but the patient will feel cramping during the procedure. The type of anesthesia used often depends upon the reason for the D&C.

To begin the procedure (which takes only minutes to perform), the doctor inserts an instrument to hold open

KEY TERMS

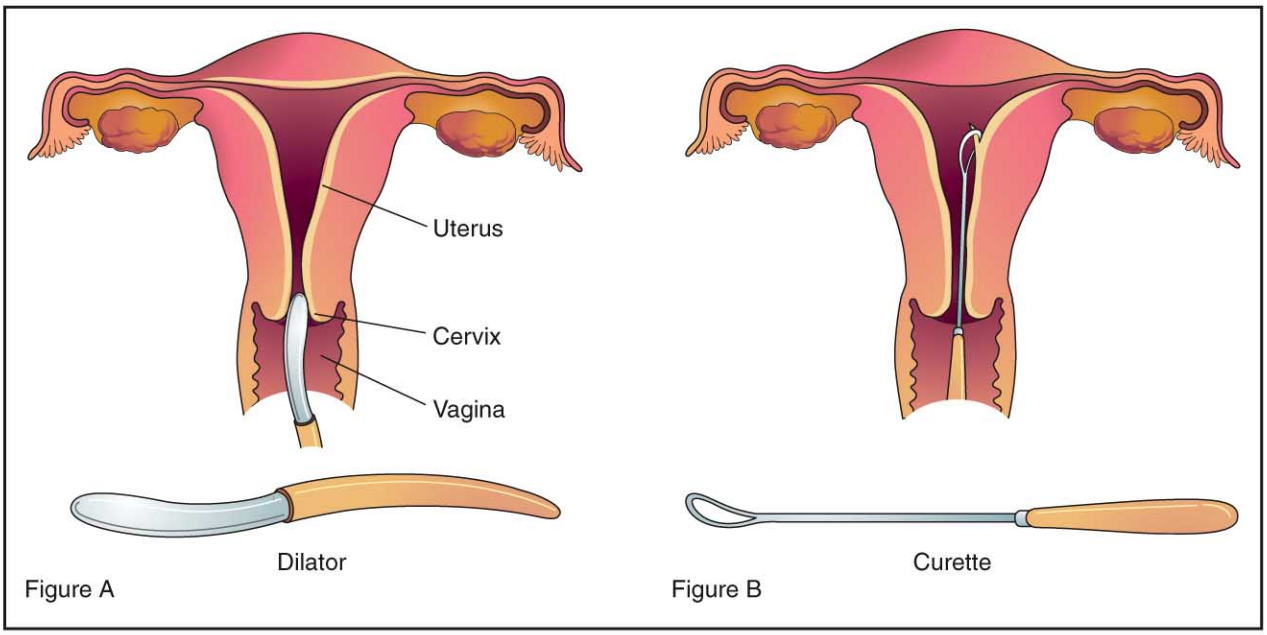
Endomerial hyperplasia—Thickening of the uterine lining. The types of hyperplasia include: simple, complex, and atypical.

Endometrial polyps—A growth in the lining of the uterus (endometrium) that may cause bleeding and can develop into cancer.

Epidural anesthesia—A type of anesthesia that is injected into the epidural space of the spinal cord to numb the nerves leading to the lower half of the body.

Hysteroscopy—A procedure in which the doctor can see the uterine lining with a tube and viewing system. This is sometimes done with a D&C.

Uterine fibroid—A noncancerous tumor of the uterus that can range from the size of a pea to the size of a grapefruit. Small fibroids require no treatment, but those causing serious symptoms may need to be removed.



Dilatation and curettage (D & C) is used primarily to diagnose and treat heavy menstrual bleeding and to diagnose endometrial polyps, uterine fibroids, uterine cancer and cervical cancer. When performing a D & C, the physician inserts a speculum to separate and hold the vaginal walls, then stretches open the cervix with a dilator. Once the cervix is dilated, the physician will insert a curette into the uterus and scrape away small portions of the uterine lining for laboratory analysis. *(Illustration by Electronic Illustrators Group. Reproduced by permission of The Gale Group.)*

the vaginal walls, and then stretches the opening of the uterus to the vagina (the cervix). This is done by inserting a series of tapering rods, each thicker than the previous one, or by using other specialized instruments. The process of opening the cervix is called dilation.

Once the cervix is dilated, the physician inserts a spoon-shaped surgical device called a curette into the uterus. The curette is used to scrape away the uterine lining. One or more small tissue samples from the lining of the uterus or the cervical canal are sent for analysis by microscope to check for abnormal cells.

Although simpler, less expensive techniques such as a vacuum aspiration are quickly replacing the D&C as a diagnostic method, it is still often used to diagnose and treat a number of conditions, especially when cancer is suspected.

Preparation

Because opening the cervix can be painful, sedatives may be given before the procedure begins. Deep breathing and other relaxation techniques may help ease cramping during cervical dilation.

Aftercare

A woman who has had a D&C performed in a hospital can usually go home the same day or the next day. Many women experience backache and mild cramps after the procedure, and may pass small blood clots for a day or so. Vaginal staining or bleeding may continue for several weeks.

Most women can resume normal activities almost immediately. Patients should avoid sexual intercourse, douching, and tampon use for at least two weeks to prevent infection while the cervix is closing and to allow the endometrium to heal completely.

Risks

The primary risk after the procedure is infection. Signs of infection include:

- fever
- heavy bleeding
- severe cramps
- foul-smelling vaginal discharge A woman should report any of these symptoms to her doctor, who can treat the infection with **antibiotics** before it becomes serious.

D&C is a surgical operation, which carries certain risks associated with general anesthesia. Rare complications include puncture of the uterus (which usually heals on its own) or puncture of the bowel or bladder (which requires further surgery to repair).

QUESTIONS TO ASK THE DOCTOR

- What are you looking for in the D&C?
- Do you recommend any special preparation before the procedure?
- How long will the procedure take?
- What is the risk of finding cancer in my case?
- What action will be taken if cancer is found?
- Will a repeat D& C be necessary?

Normal results

Results are considered normal if no unusual thickening, growths, or cancers are found. Removal of the uterine lining causes no side effects, and may be beneficial if the lining has thickened so much that it causes heavy periods. The uterine lining soon grows again normally, as part of the menstrual cycle.

Abnormal results

Some types of uterine thickening, called hyperplasia, are considered abnormal. Simple hyperplasia is a benign condition in which the uterine lining becomes thicker and with more endometrial glands. In complex hyperplasia, another condition where the uterine lining has thickened, the endometrial glands are crowded together. In 80% of cases these conditions will improve, and there is little risk of cancer. Only 1% of simple hyperplasia and 3% of complex hyperplasia will become cancerous.

Atypical hyperplasia is a more serious finding. In this type of endometrial thickening, the cells are abnormal. Twenty-nine percent of women with atypical hyperplasia develop cancer. In fact, in 17% to 25% of women with atypical hyperplasia who have a hysterectomy within one month of diagnosis, a **carcinoma** is found elsewhere in the endometrium.

A D&C is not a fool-proof procedure because only a portion of the uterine lining is sampled. Therefore, it is possible for a cancer to be missed. Because of this, patients with atypical hyperplasia must have another D&C in three or four months. Combining a hysteroscopy (a procedure where a physician can see the lining of the uterus using a special tool) with D&C may increase the accuracy of the diagnosis in some cases. However, this combination is not recommended when endometrial carcinoma is suspected because of the possibility that the hysteroscopy itself can aid in the spread of cancer through the fallopian tubes.

See also Biopsy; Endometrial cancer; Gynecologic cancers.

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Carol A. Turkington

Diphenhydramine

Definition

Diphenhydramine is an antihistamine used to treat allergies, motion sickness, allergic reactions, insomnia, cough, nausea, and phenothiazine drug-induced abnormal muscle movement.

Purpose

Diphenhydramine is frequently ordered for cancer patients to aid in controlling nausea and **itching**. It may be given after a blood transfusion to limit allergic reactions to blood products. Because of its sedating properties, diphenhydramine is often used to assist in inducing sleep. It is also used to control nausea, treat the stiffness and tremor of Parkinson's disease, and control symptoms of extrapyramidal neurologic movement disorders (tremors and abnormal involuntary movements of the muscles) caused by some drugs used to treat psychosis or **nausea and vomiting**). The drug may also be formulated as a syrup and used to relieve a cough caused by minor throat irritation due to a cold or hay fever.

In the context of cancer therapy, diphenhydramine can also be used as a pretreatment to limit the patient's reactions to radiocontrast media or to minimize the toxic side effects of such drugs as docetaxel.

Description

Diphenhydramine is an antihistamine that dries, sedates, and is distributed throughout the body. It is readily absorbed when taken by mouth, with peak action occurring about one hour after ingestion. The effects last from four to six hours. This type of drug seems to compete with histamine for receptor sites after exposure to an allergen. By blocking histamine from attaching to the receptor site, the drug decreases itchiness, a runny nose, hives, and other symptoms of an allergic reaction.

Recommended dosage

The dose should be adjusted depending on the needs of the patient and their response to the medication. Adults generally take from 25 mg to 50 mg, three to four times daily. For sleep, 50 mg at bedtime is the usual dose. Injectable diphenhydramine, 10 mg to 50 mg, may be administered through a vein or injected deep within a muscle. Some patients may require 100 mg injections. The daily dose should not exceed 400 mg. Patients should not double up on doses if one is missed.

Children weighing more than 20 pounds may take from 12.5 mg to 25 mg, three to four times daily. Children should not consume more than 300 mg in one day. The doctor may calculate a recommended dosage based on the child's weight. Parents should not double up on doses if one is missed.

Lotions or creams with diphenhydramine may be applied to the skin to relieve itching in adults and children older than two. The creams contain 1% or 2% diphenhydramine and may be used on the affected area three to four times per day. Topical diphenhydramine should not be applied to large areas of the body, blistered or oozing skin, sunburn, or lesions caused by poison ivy or chickenpox. Patients should not use topical diphenhydramine with other antihistamine-containing lotions or creams.

Precautions

Patients with angle closure glaucoma, peptic ulcer disease, bowel obstructions, an enlarged prostate, or difficulty urinating due to a blockage in the bladder should not use this medication without a doctor's order and monitoring. This drug should be used with caution in patients with asthma, heart disease, high blood pressure, or an overactive thyroid. Prior to taking this medication, patients with these conditions should discuss this medication with their doctor. Patients should not take diphenhydramine for several days prior to an allergy test. It will interfere with obtaining accurate results.

Elderly patients are especially prone to diphenhydramine's sedating effects. The drug may also cause dizziness and lower blood pressure in this population group. Patients should slowly change position from sitting or lying to standing when taking this medication.

Children also may experience drowsiness. In young children, this drug may produce the opposite effect. Pregnant women and those breast feeding should discuss the use of this and other drugs with their physician prior to use.

KEY TERMS

Allergen—Something that triggers an allergic reaction

Antihistamine—Agent that blocks or counteracts the action of histamine

Extrapyramidal movement disorders—Involuntary movements that occur as a side effect of psychiatric medications

Histamine—Substance released during allergic reactions

Side effects

Drowsiness commonly occurs after taking diphenhydramine. This effect may be more pronounced if alcohol or another central nervous system depressant, such as a tranquilizer or pain medication, is also ingested. Those taking the drug should refrain from driving or operating machinery or appliances until the medication has worn off. It also may cause dizziness, coordination difficulties, confusion, restlessness, nervousness, difficulty sleeping, blurry or double vision, ringing in the ears, headache, or convulsions.

Stomach distress also is common with diphenhydramine. Patients may develop a poor appetite, nausea, vomiting, **diarrhea** or constipation. Patients also may experience low blood pressure, palpitations, a rapid or irregular heart beat, an early onset of menstruation, frequent urination, or difficulty urinating, with urine retained in the bladder.

Diphenhydramine may also cause hives, a rash, sensitivity to the sun, and a dry mouth and nose. Thickened lung secretions are common.

A less common but potentially serious side effect of high doses of diphenhydramine is weakening or deterioration of muscle tissue. Patients should be careful not to take higher doses of the drug than their doctor recommends.

Interactions

Alcohol, pain medications, sleeping pills, tranquilizers and antidepressants may make the drowsiness associated with diphenhydramine more severe.

Diphenhydramine's drying effects may be stronger and last longer when taken with an antidepressant called an MAO inhibitor.

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United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA (463-6332). <http://www.fda.gov>.

Debra Wood, R.N.
Rebecca J. Frey, PhD

Diphenoxylate *see* **Antidiarrheal agents**

Disseminated intravascular coagulation

Description

Disseminated intravascular coagulation, or DIC, is a bleeding disorder resulting from the widespread overstimulation of the body's clotting and anticlotting mechanisms in response to illness, stress, or both. Disseminated intravascular coagulation (DIC) occurs mainly within the capillaries or the microcirculation. It is a secondary complication of a diverse group of disorders that activate, in some way, the coagulation system.

Causes

Disseminated intravascular coagulation occurs when the body's clotting mechanisms are activated throughout the body in response to an injury or a disorder, instead of being isolated to the area of initial onset. Platelets circulating throughout the body form small blood clots (thrombi) primarily in the area of the capillaries. This eventually causes the clotting factors to be used up, and none are left to form clots at the site of the injury. The presence of numerous small clots precipitates the release of clot-dissolving mechanisms, and the end result is generalized bleeding throughout the body. It is, in essence, a paradoxical situation—numerous microthrombi are being formed in the capillaries and the body reacts to dissolve these clots. It is sometimes called consumptive coagulopathy to indicate this paradox because the intravascular clotting rapidly consumes the products necessary for clotting: fibrinogen, platelets, prothrombin, and clotting factors V, VIII, and X.

Disseminated intravascular coagulation should be suspected in any individual who has an unexplained tendency toward bleeding and has experienced any clinical condition that introduces coagulation-promoting factors into the circulation. These conditions include placental abruption; retained dead fetus; amniotic fluid embolism; metastatic cancer of the pancreas, lung, stomach, or prostate; and **acute leukemia**. Any condition that also causes decreased blood flow, such as hypotension, can stimulate DIC. Widespread injury to the tissues throughout the body, as in severe burns, trauma, heat stroke, surgery, various types of infections by bacteria and fungus, snake bites, and fat embolism, can precipitate the cascade of factors to produce DIC. Excessive bleeding can appear suddenly and progress rapidly to severe or fatal hemorrhage. Signs and symptoms that appear gradually are prolonged bleeding from a venipuncture site, bleeding gums, nosebleeds, and bruising easily as well as the presence of minute, pinpoint red spots caused by bleeding under the layer of the skin.

KEY TERMS

Cryoprecipitate—A preparation of antihemophilic factor used in the management of hemophilia.

Embolism—The sudden blocking of an artery by a clot of foreign material (fat, air bubble, tissue, clump of bacteria, blood clot). This foreign material is referred to as the embolus.

Polycythemia—An increase in the total red cell mass of the blood.

Thrombus—Blood clots: an accumulation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, which frequently cause an obstruction in the circulation of blood. Microthrombi are very small blood clots.

Venipuncture—Surgical puncture of a vein.

Treatments

The objective of treatment is to determine the underlying cause of DIC and treat it, because this underlying cause predicts the probable outcome. The presence of inadequate blood components can be overcome with fresh frozen plasma and blood transfusions. Fibrinogen replacement can also occur by transfusion of blood products. When the primary disease cannot be treated, intravenous injections of **heparin**, a medication used to prevent thrombosis, are sometimes used in combination with replacement therapy. The use of heparin is, however, very controversial because it can cause bleeding itself.

Alternative and complementary therapies

Disseminated intravascular coagulation is an extremely serious condition precipitated by extraordinary events. Because it is an immediate, life-threatening situation, alternative and complementary therapies are not recommended during this phase. As an individual improves, it is important to utilize relaxation, visualization and imagery as well as vitamin and mineral supplements to promote healing.

Linda K. Bennington, C.N.S., M.S.N.

DNA *see* **Cancer genetics**

DNA flow cytometry

Definition

DNA **flow cytometry** is a method of measuring the amount of deoxyribonucleic acid (DNA, genetic material) in tumor cells and the percentage of cells actively replicating.

Purpose

DNA flow cytometric analysis is sometimes done to assess a patient's prognosis. It is used to help the physician determine how the tumor cells are likely to behave. It may also be used to monitor a patient if the tumor is expected to recur.

Description

DNA flow cytometric analysis may be performed on tissue from a **biopsy** or it may require a sample of blood or body fluid from the patient. If a blood sample is used, it will be separated into its different components and the red blood cells will be removed. If material from a biopsy is used, cells from the solid tissue will be separated from each other. The cells to be analyzed will then be mixed with a dye called propidium iodide that binds tightly to DNA. This dye gives off fluorescent light as the cells pass through the laser beam of the cytometer. The cytometer can also measure other information about the cells, such as their size.

By analyzing the amount of fluorescence that the cells emit, the pathologist can evaluate the DNA content; this is also sometimes referred to as the DNA index or **ploidy analysis**. It can also determined whether or not the cancer cells are dividing; this is called S-phase analysis. The physician sometimes uses this information to determine the patient's prognosis and choose the most effective treatment.

KEY TERMS

Aneuploid—A cell that has an irregular number of chromosomes.

Cell cycle—The events that take place during the time in which a cell replicates itself.

Diploid—A cell that has two sets (the normal number in humans) of chromosomes.

Mitosis—The process of cell division.

Preparation

If a biopsy is required, the patient should be prepared for the biopsy as suggested by the physician. Alternatively, a routine blood or body fluid sample may be required. Other special preparations are not usually necessary.

Risks

The risks associated with DNA flow cytometry are limited to those associated with blood or biopsy sample collection.

Normal results

Most cells are normally in a resting, or non-proliferating, phase of the cell cycle. During this time the cells are diploid, meaning they have two copies of each chromosome. Cells duplicate their DNA during what is called S-phase so that they can reproduce, resulting in four copies of each chromosome. The cells rest again until a period called mitosis, when they begin to divide.

Normal DNA flow cytometry results will show that most of the cells are resting and have only two copies of each chromosome. Less than 10% of the cells will be in S-

QUESTIONS TO ASK THE DOCTOR

- What type of information do you expect to learn from this test?
- Are there any alternatives to doing this test?
- Is it possible that the test may give unclear or inaccurate results?
- Are there any risks or complications that could take place?

phase. DNA flow cytometry results are usually presented in graphical form for easier analysis. A normal graph will show one large peak of resting cells, followed by a flat area and another smaller peak of cells about to divide.

Abnormal results

Abnormal results will show as several peaks of differing sizes. This means that some of the cells in the sample have extra DNA or an irregular number of chromosomes. An increased percentage of cells may be in S-phase replicating their DNA. An abnormal result does not necessarily mean malignancy; DNA flow cytometry results must be combined with other tests to diagnose malignancy. Interpretation of results is also dependent on the type of tumor being examined. In most types of cancers the presence of cells with irregular amounts of DNA is associated with a poor prognosis, but in some types of cancers, it may indicate a good prognosis.

See also Tumor grading.

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Racquel Baert, M.Sc.

Docetaxel

Definition

Docetaxel is a drug used to treat certain types of cancer. Docetaxel is available under the trade name Taxotere.

Purpose

Docetaxel is an antineoplastic agent used to treat **breast cancer** and non-small cell lung **carcinoma**.

Description

Docetaxel was approved by the Food and Drug Administration (FDA) in 1996.

Docetaxel is a synthetic derivative of the naturally occurring compound **paclitaxel**. Docetaxel is synthesized from the naturally occurring compound, 10-deacetyl baccatin III, which is extracted from the needles of yew plants. Docetaxel belongs to a group of chemicals called taxoids. The chemical structure and biological action of docetaxel is similar to that of paclitaxel.

Docetaxel promotes the formation of microtubules that do not function properly. One of the roles of normal microtubules is to aid in cell duplication. By disrupting this function, docetaxel inhibits cell reproduction.

Docetaxel is used in patients who have breast cancer that has recurred or progressed following treatment with other drugs. It is also used to treat non-small cell lung carcinoma alone, or in combination with platinum-containing drugs such as **cisplatin**. Some increases in survival times have been observed in patients treated with regiments that include docetaxel compared to control populations.

Recommended dosage

There is no known antidote for docetaxel overdose, so patients should be carefully monitored during treatment for toxicity.

Docetaxel is administered intravenously, in a dose that ranges from 60–100 mg/m^2, over one hour, once every three weeks. The initial dose may be adjusted downward depending on patient tolerance to the toxic side effects of the drug. Also, blood tests may be necessary to ensure that the bone marrow is functioning adequately to continue treatment at the recommended interval.

All patients should be pretreated with **corticosteroids** such as **dexamethasone** prior to docetaxel administration, to help prevent adverse side effects. These side

effects include severe hypersensitivity to docetaxel treatment and fluid retention. Premedication should start one day prior to docetaxel treatment and continue for three to five days.

Precautions

Docetaxel should only be used under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Special caution should be taken to monitor the toxic effects of docetaxel, especially suppression of bone marrow function and hypersensitivity reactions. Premedication to prevent hypersensitivity reactions is recommended. Minor to severe hypersensitivity reactions may occur within a few minutes of the start of treatment. Severe hypersensitivity requires treatment. Certain complications will only be possible to manage if the necessary diagnostic and treatment resources are readily available.

Because docetaxel is administered intravenously, the site of infusion should be monitored for signs of inflammation.

Adverse effects of docetaxel treatment in patients with significant liver dysfunction are more likely. High doses of treatment also may increase the likelihood and severity of adverse side effects.

Docetaxel should not be administered to patients who are known to have severe hypersensitivity to polysorbate 80, which is a component of the treatment that helps dissolve the drug.

The safety of docetaxel in children under 16 years of age has not been established.

Docetaxel can cause harm to a fetus when administered to pregnant women. This treatment should be used during pregnancy only in life-threatening situations. Women of child bearing age are advised not to become pregnant during treatment. Women should stop nursing before beginning treatment, due to the potential for serious adverse side effects in nursing infants.

Side effects

Suppression of bone marrow function is the principal adverse side effect associated with docetaxel treatment. Blood tests will allow a doctor to determine if there is adequate bone marrow function to begin or continue treatment. Hypersensitivity and fluid retention may also occur during treatment. Corticosteroids are administered prior to treatment to lessen these side effects. Ulceration of the mouth and surrounding areas is possible. Additional side effects, including **fever**, decrease in blood pressure, nausea and vomiting, **diarrhea**, pain, abnormal liver function, skin rash, nerve damage, and hair loss (alopecia) may occur.

A 2003 study showed that although docetaxel produced higher toxicities among patients in the short-term, breast cancer patients treated with docetaxel had higher survival and similar quality of life scores than those treated with paclitaxel. Although the women experienced more side effects such as reduction in white blood cells, some loss of strength, infection, and mouth ulcers, among others, the effects did not affect their quality of life over time. And the women survived longer.

KEY TERMS

10-deacetyl baccatin III—A naturally occuring compound that can be converted to docetaxel.

Hypersensitivity—An abnormally sensitive reaction to a stimulus. Similar to an allergic reaction.

Microtubles—A tubular structure located in cells that help them to replicate.

Taxoids—A complex molecule that is chemically similar to paclitaxel.

Therapeutic index—A ratio of the maximum tolerated dose of a drug divided by the dose used in treatment.

Interactions

As of 2003, no formal studies had been reported exploring interactions between docetaxel and other medications. Drugs that may alter the metabolism of docetaxel such as cyclosporine, terfenadine, ketoconazole, erythomycin and troleandomycin should be used with caution due to the potential for interactions.

Resources

PERIODICALS

"Comparison Study Finds Better Overall Response Rate, Survival with Docetaxel." *Drug Week* October 17, 2003: 67.

"Study Shows Improved Survival Rates, Time to Disease Progression with Docetaxel." *Women's Health Weekly* December 25, 2003: 33.

Marc Scanio
Teresa G. Odle

Docusate *see* **Laxatives**

Dolasetron *see* **Antiemetics**

Double contrast barium enema *see* **Barium enema**

Doxorubicin

Definition

Doxorubicin, which kills cancer cells, is among the most widely used **chemotherapy** drugs. It is also known by its trade name, Adriamycin.

Purpose

This anticancer drug may be used to fight several different cancers: **breast cancer**, **ovarian cancer**, gastric (stomach) cancer, **thyroid cancer**, lung cancer, **testicular cancer**, and **endometrial cancer**. In addition it may be used against Hodgkin's and non-Hodgkin's **lymphoma**, acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), **sarcomas** of the soft tissue, sarcomas of the bone (osteosarcomas), **neuroblastoma**, **Wilms' tumor**, small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC).

Because doxorubicin is used to treat so many different cancers, a complete description of how it may be combined with other medications in the treatment of each of the cancers cannot be given here. A few examples follow: In the treatment of Hodgkin's disease, for instance, one widely used chemotherapy regimen is the so-called ABVD, which consists of doxorubicin, **bleomycin**, **vinblastine**, and **dacarbazine**. Another is the so-called MOPP/ABV, which consists of **mechlorethamine**, **vincristine** (Oncovin), prednisone, **procarbazine**, doxorubicin, bleomycin, and vinblastine. Yet another is the so-called EVA: **etoposide**, vinblastine, and doxorubicin. Still another is the so-called EPOCH, which consists of etoposide, vincristine, doxorubicin, **cyclophosphamide**, and prednisone.

Doctors may treat stage III and IV non-Hodgkin's lymphoma with the so-called m-BACOD chemotherapy regimen, which consists of **methotrexate**, bleomycin, doxorubicin, cyclophosphamide, vincristine, and **dexamethasone**. Yet another regimen called the ProMACE-CytaBOM, which consists of cyclophosphamide, doxorubicin, etoposide, prednisone, **cytarabine**, bleomycin, vincristine, methotrexate, and **leucovorin**.

Complete remission (CR) is the total elimination of all diseased cells detectable following therapy. Continuous complete remission is CR that continues indefinitely. In the treatment of **acute lymphocytic leukemia** (ALL), it has been found that the likelihood that continuous complete remission will be achieved is increased if the patient receives at least three drugs. Two of these are usually prednisone and vincristine. The third may be doxorubicin.

Description

Doxorubicin is a DNA-binding anticancer drug and belongs to an anthracycline antibiotic, although doctors do not use this drug to attack microbial infections.

Recommended dosage

Between 60 and 90 milligrams per square meter of doxorubicin are administered via a single intravenous (IV) injection every 21 days. Alternately, between 20 and 30 milligrams per square meter per day may be given via IV for three days every three to four weeks. Alternately, 20 milligrams per square meter may be given via IV weekly. The dose of doxorubicin used depends upon which regimen for cancer is being followed.

For example, in the treatment of **acute myelocytic leukemia** (AML), 30 milligrams per square meter may be given over a period of three days. When the medication is used in the treatment of breast cancer, one chemotherapy regimen is the so-called AC, which consists of doxorubicin plus cyclophosphamide. A total of 60 milligrams of doxorubicin per square meter are given per day. AC is then repeated every 21 days.

Another chemotherapy regimen used for breast cancer is known as either FAC or CAF: **fluorouracil**, doxorubicin, and cyclophosphamide. In this regimen, 50 milligrams of doxorubicin are given per square meter per day.

Doxorubicin is not given by mouth, as an insufficient amount of the medication would be transported through the stomach wall if this were done. Rather this medication is usually administered through an intravenous (IV) procedure. Patients with liver problems may be given a reduced dose of doxorubicin.

Precautions

Doxorubicin may cause serious heart problems. To prevent these, doctors may limit the amount of doxorubicin given to each patient so that the total amount of doxorubicin a patient receives over her or his entire lifetime is 550 milligrams per square meter, or less. An encouraging recent development is that medication is now available that appears to help protect the patient's heat from the effects of doxorubicin. This new medication is called **dexrazoxane** (Zinecard).

Side effects

Patients may develop problems with heart rhythms while doxorubicin is being taken. In addition, a serious heart illness known as heart failure may develop later. Some patients develop heart failure more than 20 after having received doxorubicin.

Studies have shown that the use of the new medication dexrazoxane (Zinecard) helps protect the patient's heart from the harmful effects of doxorubicin. However, dexrazoxane itself has side effects. For example, it may intensify the reduction of blood cells that may occur with doxorubicin therapy. In addition, it may make doxorubicin less effective in attacking cancer. Dexrazoxane is used only in patients being treated for breast cancer and only in patients who have already been given more than half of the total lifetime amount of doxorubicin they should ever receive.

The activity of the bone marrow in producing blood cells may be harmed by doxorubicin. Side effects affecting the heart and bone marrow may cause doctors to lower the dose of doxorubicin. Other side effects associated with doxorubicin are nausea and vomiting, stomach problems, eye problems, loss of appetite (anorexia), and hair loss (alopecia). Blistering may result if bleeding occurs. In addition, the medication has a harmless side effect about which patients should be forewarned: the urine and tears may have a red color.

Patients receiving doxorubicin in conjunction with certain other anticancer drugs may, very rarely, develop a type of leukemia.

Bob Kirsch

Dronabinol *see* **Antiemetics**

Droperidol *see* **Antiemetics**

Drug resistance

Definition

Drug resistance refers to the ability of an organism, such as the HIV virus, the tuberculosis bacillus (TB), or cancer, to overcome the effects of a drug prescribed to destroy it. Well-known examples are the resistance of the HIV virus to AZT, or that of TB to **antibiotics**. Resistance has been observed to occur with every anti-HIV drug prescribed. According to the Mayo Clinic in Rochester, Minnesota, drug resistance may have played a role in the 58% rise in infectious disease deaths observed in the United States between 1980 and 1992.

Due to the immunocompromised state of cancer patients caused by the cancer treatment effect, infections with viruses and bacteria are commonplace and infectious disease treatment is paramount.

Causes

A virus like HIV becomes resistant to drugs because it has the ability to mutate. This happens because a typical virus creates billions of new viruses in the body every day—viruses that are replicas of itself. However, these replicas are not always perfect. In this daily production of billions of viruses, several small differences can occur in some of the new viruses. These differences are called *mutations*. When such mutations occur on that part of the virus that the drug is designed to chemically attach to, the drug's action is effectively stopped because it cannot attach. When a drug no longer works against its target, this is called drug resistance and the virus that the drug can no longer destroy is said to be resistant to the drug.

An example of drug resistance is a patient with AIDS. The patient may have a few HIV viruses that mutate in such a way that prevents AZT from working on those mutated viruses. The drug will still work against the HIV that has not mutated, eventually destroying it. However, reproduction of the mutated virus is then unchecked, and the infection keeps spreading as the mutated virus makes more copies of itself, which are also resistant to AZT. After some time, this mutated AZT-resistant HIV will be the only type of HIV left, and AZT will no longer work for that patient.

A similar scenario may occur with cancer drug resistance. Since the early 1970s, multiple drug resistance (MDR) has also been known to exist in several types of cancer cells. It now appears that certain cancers have the capacity to resist the cytotoxic (toxic to cells) effects of cancer **chemotherapy**, probably due to genetic abnormalities in the cancer cells. Normal tissues never develop resistance to chemotherapy. Initially, sensitive cancer cells are destroyed by chemotherapy but since mutated cancer cells are allowed to replicate (unlike normal cells that are destroyed when defective) these mutated cancer cells are no longer sensitive to some chemotherapy.

Resistance of cytomegalovirus (CMV) against antiviral drugs is another example showing that drug resistance is becoming an increasingly serious medical problem.

Like viruses, bacteria can also become drug resistant. Every time a patient takes an antibiotic, such as penicillin, to fight a bacterial infection, the antibiotic destroys most of the bacteria. However, a few tough germs may survive—either by mutating like viruses or by obtaining resistance genes from other bacteria. These survivors can then reproduce quickly, creating new drug-resistant bacteria. As is the case with mutated viruses, the presence of these resistant bacterial strains usually means that the next infection will not be cured by the first-choice antibiotic prescribed by the doctor.

Some bacteria that have already become resistant to antibiotic attack include:

- Staphylococcus aureus: This bacterium causes the majority of infections in patients in U.S. hospitals. It spreads and infects cuts, burns, skin, as well as surgical wounds. Since 1996, at least four patients have been reported to be infected with a strain that was partially resistant to normal doses of the most powerful antibiotic available, vancomycin.
- Streptococcus pneumoniae: This bacterium causes **pneumonia**, meningitis, and ear infections. According to the Mayo Clinic, it has also become partially resistant to antibiotics of the penicillin family.
- Enterococcus: This bacterium can cause everything from urinary tract to heart valve infections and it is also becoming increasingly antibiotic-resistant, including vancomycin-resistant.

If a virus or bacteria mutates at a specific location that represents the target for the drug to attach to, then modifying the drug so as to have it attach at a different place will succeed in overcoming the drug resistance. In the case of HIV, compiled databases of mutations in HIV genes that confer resistance to anti-HIV drugs are available to assist researchers in the design and production of new drugs.

Treatments

The strategies used to overcome drug resistance depend upon the nature of the organism causing the infection but generally involve the following steps:

- Accurate and rapid diagnosis: Swift identification and treatment—the sooner the infectious organism is detected and correctly identified, the higher the chances that it will not become drug resistant since it will have less time to mutate.
- Drug combination: New combinations of drugs can be very effective. Given a mixture of mutated and unmutated pathogens, a drug "cocktail" is likely to contain a drug that may be effective against a new mutated form of the virus, thus preventing it from making billions of new copies every day. The less virus created, the less chance of further mutations occurring.

KEY TERMS

AIDS (Acquired Immunodeficiency Syndrome)—A state of severe immune suppression caused by the HIV virus. A diagnosis of AIDS is given to a patient infected with HIV and who also experiences at least one condition from a list compiled by the Center for Disease Control and Prevention (CDC), as for example an infection with cytomegalovirus (CMV) or a cancer such as Kaposi's sarcoma.

Antibiotic—A drug that slows bacterial growth or kills bacteria.

Antiviral drug—A drug that slows viral growth or kills viruses.

AZT (Retrovir, zidovudine, ZDV)—The first drug licensed to treat HIV. It is almost always used in combination with other anti-HIV drugs. AZT is also used to prevent transmission of HIV from mother to fetus.

Bacterium—A tiny microorganism that reproduces by cell division. It can be shaped like a rod, sphere, or spiral and is found virtually everywhere. Many types of bacteria cause infection and disease.

CMV (Cytomegalovirus)—A virus that belongs to the herpes virus family and is present as a silent infection in almost everyone. CMV often becomes activated in people with AIDS.

Cytoxic—A substance toxic (poisonous) to cells.

Gene—The part of DNA responsible for determining a person's characteristics. It also transfers information from old cells to new cells.

Gene therapy—The use of genes to treat cancer and other diseases.

Immune system—The system within the body, consisting of many organs and cells, that recognizes and fights foreign cells and disease.

Pathogen—Anything capable of causing disease, usually a virus or bacterium, but it also refers to chemical substances, such as asbestos.

Tuberculosis—An infectious disease of the lungs caused by a type of bacterium called amycobacterium. Symptoms include weight loss, fever, and cough, often with blood-streaked mucus. Tuberculosis is highly contagious.

- New drugs: There is a problem facing all the strategies used to overcome drug resistance and it is that drugs have to be given at high—and sometimes toxic—doses, and also in combinations that have become quite expensive. Increasingly, they also must be taken on schedules that are difficult to follow by patients. Even then, new varieties of resistant strains still appear. There is, therefore, an urgent need to understand how drug resistance develops at the molecular level, and to use this understanding to develop more effective drugs.

See also AIDS-related cancers.

Resources

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National Cancer Institute, HIV Drug Resistance Program. NCI-Frederick, Building 535, Room 109, P.O. Box B, Frederick, MD 21702-1201. Phone:(301)846-1168. <http://www.ncifcrf.gov/hivdrp>.

U. S. Food and Drug Administration. 5600 Fishers Lane, Rockville, MD 20857. Phone:(888)INFO-FDA [(888)463-6332] <http://www.fda.gov/default.htm>.

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Monique Laberge, Ph.D.

Dryness of the mouth, mouth dryness
see **Xerostomia**

Ductogram

Definition

A ductogram, also called a galactogram, is a special type of mammogram used for imaging the breast ducts. It can aid in diagnosing the cause of abnormal nipple discharges.

Purpose

The purpose of a ductogram is to locate the origin of an abnormal discharge from the nipple of the breast.

Precautions

Women who are pregnant should not undergo a ductogram without adequate protection of the abdomen from the x rays that are used in this test.

Description

A ductogram is performed by first cleansing the nipple and areola with an antiseptic. The radiologist performing the test then presses gently on the nipple to determine which duct is leaking fluid. Once the leaking duct has been identified, a small needle (cannula) is inserted into that duct. A dye is then injected into the leaking duct and an **x ray** similar to a mammogram is performed.

This test is performed in a mammography or breast imaging facility, either in a hospital department or an outpatient x-ray center. During this procedure, the patient is in a sitting, standing, or horizontal position depending on the x-ray equipment available at the testing center where the ductogram is to be performed. The x-ray camera may change position during the study, but the patient is usually stationary. The procedure typically takes 30 to 60 min-

KEY TERMS

Cannula—A small tube or hollow needle designed for insertion into a duct.

Ductogram—A special type of mammogram used diagnosing the cause of abnormal nipple discharges.

Pathologic—Diseased or abnormal.

QUESTIONS TO ASK THE DOCTOR

- Were any abnormalities detected?
- What future care is necessary?
- What are the risks and precautions of any further procedures?

utes. It is important for the patient not to move except when directed to do so by the technologist.

Preparation

There is usually little or no preparation required of the patient for a ductogram. Prior to the test, the patient should not attempt to express a discharge from the affected nipple or nipples. Jewelry or metallic objects that may interfere with the x-ray image should be removed for the duration of the ductogram. No deodorant or powder should be used as this can interfere with the test.

If the nipple drainage suddenly stops on the day of the ductogram, the patient should notify her health care provider prior to undergoing this test.

Aftercare

No special care is required after the test. Fluids are encouraged after the procedure to aid in the excretion of the dye from the body.

Risks

The risks of a ductogram are very low. Most ductograms use the same amount of radiation as a conventional x ray. Side effects or negative reactions are very rare. Possible side effects include pain, infection, and bleeding from the nipple where the cannula was inserted.

Normal results

A normal ductogram shows the expected distribution of the dye material within the ducts of the breast and no unusual shape or size of the scanned tissue.

Abnormal results

An abnormal ductogram shows an abnormality within the ducts of the breast that may be causing the pathologic discharge of fluid from that breast. If an abnormality is identified, additional procedures, including surgery, may be necessary.

Resources

ORGANIZATIONS

American Cancer Society. (800) ACS-2345. <http://www.cancer.org>.

National Alliance of Breast Cancer Organizations (NABCO). 9 East 37th St., 10th Floor, New York, NY 10016. (888) 806-2226. <http://www.nabco.org>.

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Paul A. Johnson, Ed.M.

Duplex ultrasound *see* **Ultrasonography**

Dysplastic nevus syndrome *see* **Melanoma**

E

Eaton-Lambert syndrome

Description

Eaton-Lambert syndrome, also called Lambert-Eaton myasthenic syndrome (LEMS), is a rare disorder affecting the muscles and nerves. LEMS is known to be associated with small cell lung cancer. It may also be associated with cancers such as **lymphoma**, non-Hodgkin's lymphoma, T-cell leukemia, non-small cell lung cancer, **prostate cancer**, and **thymoma**.

The primary symptom of LEMS is muscular weakness or paralysis that varies in intensity and location throughout the body. Other symptoms of LEMS include tingling sensations on the skin, double vision, difficulty maintaining a steady gaze, and dry mouth or difficulty in swallowing.

The first signs of LEMS tend to be:

- changes in vision
- decreased posture and muscle tone
- difficulty in chewing or swallowing
- difficulty in climbing stairs
- difficulty in lifting simple objects
- speech impairment
- a drooping head
- fatigue
- and/or a need to use hands to get up from a sitting or lying position

LEMS is often misdiagnosed as **myasthenia gravis** because of the similarities between the symptoms of these two disorders.

Causes

The symptoms of LEMS are the result of an insufficient release of neurotransmitter by nerve cells. Neurotransmitter is a chemical which passes signals from the nerve cells to the muscles in order for the muscles to move. The decreased level of neurotransmitter causes a muscle reaction to the nerve signal that is lower than normal. The underlying cause of the lower-than-normal neurotransmitter release seen in LEMS patients is believed to be related to a malfunction of the patient's own immune system (an autoimmune reaction).

This autoimmune reaction is caused by antibodies that a patient produces in response to small cell lung cancer, or one of the other cancers associated with LEMS.

Since continued use of the muscles may lead to a build-up of the neurotransmitter to normal levels, symptoms of LEMS can often be lessened or alleviated by use of the affected muscles. Myasthenia gravis, another disorder that has symptoms similar to LEMS, is caused by a blockage of neurotransmitters by antibodies. Symptoms of myasthenia gravis do not improve with continued muscle use. The improvement in symptoms that is observable in LEMS patients often helps to differentiate LEMS from myasthenia gravis.

LEMS is aggravated by neuromuscular blocking agents used during surgery; certain **antibiotics**, such as aminoglycoside and fluoroquinolone; magnesium; calcium channel blockers; and iodinated intravenous contrast agents used for medical imaging.

Treatments

The goal of treatment for LEMS patients is to improve muscle strength while also treating the cancer or other underlying disorder that is causing LEMS.

When possible, patients affected with LEMS should undergo a physical therapy program that is tailored to their health status and abilities. This may include stretching and flexibility manuevers as well as light strength and cardiovascular exercises. Symptoms of LEMS tend to be aggravated by prolonged exercise, so any physical therapy undertaken should be relatively short in duration.

KEY TERMS

Autoimmune reaction—An immune reaction in which the body attacks healthy tissue, mistaking it for a foreign antigen.

Neurotransmitter—A chemical that is released at the end of a nerve to transmit a signal to another nerve or to a muscle.

Plasmapheresis—Also called plasma replacement, this technique is used to replace a patient's blood plasma, usually with donated plasma.

Some LEMS patients are not able to undergo physical therapy because of their current state of health. In these cases, plasmapheresis (also called plasma exchange), a procedure in which blood plasma is removed from the patient and replaced, may be recommended. This procedure can be effective in a majority of LEMS patients.

Medications that suppress the **immune response** or that suppress the antibodies responsible for the weakness have also been shown to improve LEMS symptoms in some patients.

Alternative and complementary therapies

Yoga and other stretching exercises may be effective treatments for alleviating the physical symptoms of LEMS patients. Some LEMS patients also report improvement of symptoms after deep body massage or hydrotherapy.

Resources

ORGANIZATIONS

Muscular Dystrophy Association. 3300 E. Sunrise Dr., Tucson, AZ 85718. (800) 572-1717. <http://www.mdausa.org/>.

Myasthenia Gravis Foundation of America, Inc. 5841 Cedar Lake Road, Suite 204, Minneapolis, MN 55416. (800) 541-5454. <http://www.myasthenia.org/>.

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Paul A. Johnson, Ed.M.

Edatrexate

Definition

Edatrexate is an investigational (experimental) medicine similar to **methotrexate** used to stop growth of cancer and formation of new cancer cells.

Purpose

Edatrexate has been shown to have anticancer activity in research studies in patients with lung cancer, head and neck cancer, **breast cancer**, and non-Hodgkins lymphoma.

Description

Edatrexate is an anticancer drug that belongs to a family of drugs called antimetabolites. It is an antagonist of **folic acid** closely related to methotrexate in its structure and antitumor activity. However, edatrexate has several potential advantages over methotrexate, including better transport across cancer cell membranes (walls surrounding cancer cells), increased selectivity for tumor cells, and greater antitumor effect. Edatrexate inhibits formation of genetic material and reproduction of cancer cells by inhibiting a certain enzyme needed to make folic acid. Without folic acid, formation of protein and new genetic material in cancer cells cannot occur. Unlike methotrexate, edatrexate has additive activity when used with **cisplatin** (a **chemotherapy** agent often used to treat non-small cell lung cancer) in animal studies. It also showed additive anticancer effects with **cyclophosphamide**, **paclitaxel** and **docetaxel**.

Edatrexate has been used in combination with paclitaxel, cisplatin, clyclophosphamide, mitomycin, or **vinblastine** in research studies. **Leucovorin** has been shown to be effective in reducing edatrexate side effects, but it may also decrease its antitumor effectiveness.

KEY TERMS

Bone marrow—The tissue filling the cavities of bones.

Non-Hodgkin's lymphoma—Lymphomas are some of the most treatable cancers with cure rates around 50% in 1990's. Non-Hodgkin's lymphoma mainly affects people over 50 years of age and has been more difficult to treat than the Hodgkin's type. There has been an increase in non-Hodgkin's lymphoma cases in the last two decades in patients with HIV.

Recommended Dosage

Adults

SOLID TUMORS (LUNG, BREAST, HEAD AND NECK CANCER) Doses vary between different chemotherapy protocols. The most commonly used dose in research studies was 40-80 mg per square meter of body surface area given as intravenous infusion once a week. Maximum tolerated dose when edatrexate was used in combination with paclitaxel was 120 mg per meter square per week.

Children

There is no data available on dosing and use of edatrexate in children.

Precautions

To maximize treatment effects, patients receiving edatrexate should observe certain guidelines. Including any modifications given by the oncologist, these guidelines should include regular visits with the oncologist and laboratory testing for white blood cell count, kidney, liver, and bone marrow function. Patients should avoid any immunizations not approved or prescribed by the oncologist, and they should avoid contact with individuals taking or who have recently taken oral polio vaccine, or individuals who have an active infection. When necessary, patients should wear a protective facemask, and patients should avoid prolonged or direct exposure to sunlight, as some patients experience an increased sensitivity. Patients should also ask for specific instructions on oral hygiene procedures to reduce the risk of gum abrasion, and avoid touching the eye and nasal areas unless hands have been properly washed immediately prior to contact. To reduce bleeding and bruising complications, patients should exercise extreme caution when handling sharp instruments and decline participation in contact sports. Prior to treatment, the patient's medical history should be thoroughly reviewed to avoid complications that might arise from previous conditions such as gout, kidney stones or kidney disease, liver disease, chickenpox, shingles, intestinal blockage, colitis, suppressed immune system, stomach ulcers, mouth sores, or a history of allergic reactions to various drugs.

The oncologist should also be made aware if the patient is pregnant or if there is the possibility the patient might be pregnant, or if the patient is a breast-feeding mother. Only prescribed medications or over the counter (OTC) drugs approved by the oncologist should be taken by a patient receiving edatrexate.

Side effects

The side effect profile of edatrexate is similar to that of methotrexate, with mouth ulcers as the dose-limiting toxicity. Other side effects include bone marrow suppression and decreased formation of all blood elements, **diarrhea**, skin rash, nausea, vomiting, inflammation of the lungs (pneumonitis) and mild increase in liver function tests.

Interactions

There is no published information available at this point about any potential drug or food interactions with edatrexate. As a general rule, **vaccines** should be avoided due to the immunosuppressive action of edatrexate, and alcohol should be avoided to reduce the risk of liver complications.

Olga Bessmertny, Pharm.D.

Endocrine system tumors

Definition

The group of tumors that are associated with the hormone-secreting (endocrine) glands of the body.

Description

The glands in the body that make and secrete hormones comprise the endocrine system. All endocrine glands secrete hormones directly into the bloodstream, where they travel to a target organ or cell to trigger a specific reaction. These glands are primarily involved in controlling many of the slow and long-term activities in

Endocrine system tumors

Pituitary tumors
Thyroid tumors
Parathyroid tumors
Endocrine pancreatic tumors, including gastrinoma, insulinoma, and glucagonoma
Adrenal tumors, including pheochromocytoma and adrenocortical carcinoma
Ovarian tumors
Testicular tumors
Multiple endocrine gland tumors (tumors on several endocrine glands at once)

the body, such as growth, sexual development, and regulation of blood levels for many important proteins and essential chemical elements.

Endocrine glands are found in the head and neck region, the abdominal region, and the pelvic area (the region where the reproductive organs are located). The following are the main endocrine glands of the body:

- Pituitary gland. Found at the base of the brain, this small gland is important because it secretes several hormones that control the activity of other endocrine glands.
- Thyroid gland. Situated in the front of the neck, in the region of the Adam's apple, this gland secretes hormones that regulate body temperature, heart rate, and metabolism.
- Parathyroid glands. These four glands, with a pair on either side of the thyroid gland in the neck region, produce parathyroid hormone, which helps control the level of calcium in the blood.
- Pancreas. Found close to the stomach in the abdominal region, the pancreas contains two groups of cells. One group functions as an exocrine gland, secreting digestive enzymes into the intestines through a duct. The other, known as islets of Langerhans (or islet cells), functions as an endocrine gland and secretes hormones that control blood sugar levels and aid digestion.
- Adrenal glands. These two glands, one located above each kidney, secrete hormones that prevent inflammation and help regulate blood pressure, blood sugar levels, and metabolism.
- Ovary. A woman has two small ovaries in the pelvic area. They contain the egg cells and secrete the hormones progesterone and estrogen. These hormones have many functions, including controlling the onset of puberty, the timing of menstruation, and the changes associated with pregnancy.
- Testis (also called testicle). Men typically have two testes located outside the body in the lower pelvic area. They produce sperm and the hormone **testosterone**, which signals the onset of puberty, maintains the expression of male characteristics, such as facial hair, and stimulates sperm production.

Endocrine system tumors are rare. Although certain types are likely to be diagnosed as malignant (cancerous), endocrine tumors are often noncancerous (benign). Each year endocrine system cancers account for only around 4% of all new cancer cases in the United States. In 2001, it is expected that 53,460 Americans will develop an endocrine system cancer, resulting in an estimated 16,600 deaths.

The most common cancers of the endocrine system are **ovarian cancer** and **thyroid cancer**. Ovarian cancer represents about 44% of all endocrine system cancers and affects eight out of every 100,000 American women. New cases of ovarian cancer in 2001 will likely reach over 23,000, and nearly 13,000 will die from the disease. Roughly six out of every 100,000 Americans develop thyroid cancer, which accounts for 36% of all endocrine system cancers. It is estimated that 19,000 new cases will be diagnosed in 2001 and result in 1,300 deaths. Other malignant endocrine tumors are much rarer. **Testicular cancer** affects about two out of every 100,000 American men, while the remaining cancer types combined affect roughly one out of every 100,000 Americans.

Many benign and malignant endocrine tumors are treatable with a combination of surgery and medication, and the survival rates for many endocrine cancers is good. Two exceptions are ovarian cancer and **adrenocortical carcinoma**, a tumor of the adrenal gland. About 50% of ovarian cancer patients and 40% of those diagnosed with an adrenocortical carcinoma will survive five years or more after the initial diagnosis. These cancers have poor survival rates because they are usually first diagnosed after they have spread or reached an advanced stage. Among the different cancers, thyroid cancer and testicular cancer have some of the better 5-year survival rates; both approach 95%.

Symptoms of many endocrine tumors are associated with the excessive secretion of hormones. Hormone-producing tumors are called functional tumors, while those that do not secrete hormones are called nonfunctional tumors. Both types are potentially malignant.

Types of cancers

Proceeding from the head region to the pelvic area, endocrine system tumors include:

- Pituitary tumors. These tumors are classified by the type of hormone they secrete. They are rarely malig-

KEY TERMS

Endocrine gland—Any gland that makes hormones and secretes them directly into the bloodstream.

Exocrine gland—Any gland that secretes substances outward through a duct into a body cavity or onto a body surface (e.g., sweat glands and salivary glands).

Germ cell—Any cell in the body that eventually produces either a mature egg cell (female) or a mature sperm cell (male).

Inherited disorder—A disease that has a tendency to occur within a family. A disorder may be acquired due to a gene or genes that are passed from parent to child.

nant but can cause heath problems, including visual complications. One type of tumor results in **Cushing's syndrome**.

- Thyroid tumors. Only 5% of the tumors found on the thyroid are malignant. A malignant tumor can indicate one of the four types of thyroid cancer.
- Parathyroid tumors. Around 5% are malignant and result in a diagnosis of **parathyroid cancer**. Overproduction of parathyroid hormone, a condition known as hyperparathyroidism, is a common condition associated with both benign and malignant tumors. Untreated, hyperparathyroidism can result in osteoporosis (bones become brittle and fracture easily), kidney stones, peptic ulcers, and nervous system problems.
- Endocrine pancreatic tumors. Benign and malignant tumors are often treatable with surgery. Malignant tumors are rare. The most common types of tumors are a gastrinoma, which is associated with **Zollinger-Ellison syndrome**, insulinoma, and glucagonoma.
- Adrenal tumors. One type of tumor, a **pheochromocytoma**, is found on the inner part of the adrenal gland (the adrenal medulla). About 10% are malignant. An adrenocortical carcinoma is a malignant tumor on the outer part of the gland (adrenal cortex), and a common symptom is the occurrence of Cushing's syndrome. Both tumors are very rare.
- Ovarian tumors. Tumors can develop in the egg cells inside the ovary (**germ cell tumors**), but most occur in the cells lining the outside of the ovary, and most of these tumors are benign.
- Testicular tumors. Tumors can occur in one or both of the testes. Over 90% develop in the germ cells and only 4% involve the endocrine cells of the testes.
- Multiple endocrine gland tumors. Some disorders result in the simultaneous occurrence of tumors on several endocrine glands. Many of these are inherited disorders, including **multiple endocrine neoplasia syndromes**, **von Hippel-Lindau syndrome**, and von Recklinghausen's neurofibromatosis.

See also Adenoma; Craniopharyngioma; Neuroendocrine carcinomas.

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Monica McGee, M.S.

Endometrial cancer

Definition

Endometrial cancer develops when the cells that make up the inner lining of the uterus (the endometrium) become abnormal and grow uncontrollably.

Description

Endometrial cancer (also called uterine cancer) is the fourth most common type of cancer among women and the most common gynecologic cancer. Approximately 34,000 women are diagnosed with endometrial cancer each year. In 1998, approximately 6,300 women died from this cancer. Although endometrial cancer generally occurs in women who have gone through menopause and are 45 years of age or older, 30% of the women with endometrial cancer are younger than 40 years of age. The average age at diagnosis is 60 years old.

The uterus, or womb, is the hollow female organ that supports the development of the unborn baby during pregnancy. The uterus has a thick muscular wall and an inner lining called the endometrium. The endometrium is very sensitive to hormones and it changes daily during

the menstrual cycle. The endometrium is designed to provide an ideal environment for the fertilized egg to implant and begin to grow. If pregnancy does not occur, the endometrium is shed causing the menstrual period.

More than 95% of uterine cancers arise in the endometrium. The most common type of uterine cancer is adenocarcinoma. It arises from an abnormal multiplication of endometrial cells (atypical adenomatous hyperplasia) and is made up of mature, specialized cells (well-differentiated). Less commonly, endometrial cancer arises without a preceding hyperplasia and is made up of poorly differentiated cells. The more common of these types are the papillary serous and clear cell carcinomas. Poorly differentiated endometrial cancers are often associated with a less promising prognosis.

Demographics

The highest incidence of endometrial cancer in the United States is in Caucasians, Hawaiians, Japanese, and African Americans. American Indians, Koreans, and Vietnamese have the lowest incidence. African–American and Hawaiian women are more likely to be diagnosed with advanced cancer and, therefore, have a higher risk of dying from the disease.

Causes and symptoms

Although the exact cause of endometrial cancer is unknown, it is clear that high levels of estrogen, when not balanced by progesterone, can lead to abnormal growth of the endometrium. Factors that increase a woman's risk of developing endometrial cancer are:

- Age. The risk is considerably higher in women who are over the age of 50 and have gone through menopause.
- Obesity. Being overweight is a very strong risk factor for this cancer. Fatty tissue can change other normal body chemicals into estrogen, which can promote endometrial cancer.
- Estrogen replacement therapy. Women receiving estrogen supplements after menopause have a 12 times higher risk of getting endometrial cancer if progesterone is not taken simultaneously.
- Diabetes. Diabetics have twice the risk of getting this cancer as nondiabetic women. It is not clear if this risk is due to the fact that many diabetics are also obese and hypertensive. One 1998 study found that women who were obese and diabetic were three times more likely to develop endometrial cancer than women who were obese but nondiabetic. This study also found that nonobese diabetics were not at risk of developing endometrial cancer.
- Hypertension. High blood pressure (or hypertension) is also considered a risk factor for uterine cancer.
- Irregular menstrual periods. During the menstrual cycle, there is interaction between the hormones estrogen and progesterone. Women who do not ovulate regularly are exposed to high estrogen levels for longer periods of time. If a woman does not ovulate regularly, this delicate balance is upset and may increase her chances of getting uterine cancer.
- Early first menstruation or late menopause. Having the first period at a young age (a 1997 *Pediatrics* article identified the mean age of menses as 12.16 years in African American girls and 12.88 years in white girls) or going through menopause at a late age (over age 51 according to a 2001 *Prevention* article) seem to put women at a slightly higher risk for developing endometrial cancer.
- **Tamoxifen**. This drug, which is used to treat or prevent **breast cancer**, increases a woman's chance of developing endometrial cancer. Tamoxifen users tend to have more advanced endometrial cancer with an associated poorer survival rate than those who do not take the drug. In many cases, however, the value of tamoxifen for treating breast cancer and for preventing the cancer from spreading far outweighs the small risk of getting endometrial cancer.
- Family history. Some studies suggest that endometrial cancer runs in certain families. Women with inherited mutations in the BRCA1 and BRCA2 genes are at a higher risk of developing breast, ovarian, and other **gynecologic cancers**. Those with the hereditary nonpolyposis colorectal cancer gene have a higher risk of developing endometrial cancer.
- Breast, ovarian, or **colon cancer**. Women who have a history of these other types of cancer are at an increased risk of developing endometrial cancer.
- Low parity or nulliparity. Endometrial cancer is more common in women who have born few (low parity) or no (nulliparity) children. The high levels of progesterone produced during pregnancy has a protective effect against endometrial cancer. The results of one study suggest that nulliparity is associated with a lower survival rate.
- Infertility. Risk is increased due to nulliparity or the use of fertility drugs.
- Polycystic ovary syndrome. The increased level of estrogen associated with this abnormality raises the risk of cancers of the breast and endometrium.

The most common symptom of endometrial cancer is unusual vaginal spotting, bleeding or discharge. In women who are near menopause (perimenopausal), symptoms of endometrial cancer could include bleeding between periods (intermenstrual bleeding), heavy bleeding that lasts for

more than seven days, or short menstrual cycles (fewer than 21 days). For women who have gone through menopause, any vaginal bleeding or abnormal discharge is suspect. Pain in the pelvic region and the presence of a lump (mass) are symptoms that occur late in the disease.

Diagnosis

If endometrial cancer is suspected, a series of tests will be conducted to confirm the diagnosis. The first step will involve taking a complete personal and family medical history. A physical examination, which will include a thorough pelvic examination, will also be done.

The doctor may order an endometrial **biopsy**. This is generally performed in the doctor's office and does not require anesthesia. A thin, flexible tube is inserted through the cervix and into the uterus. A small piece of endometrial tissue is removed. The patient may experience some discomfort, which can be minimized by taking an anti-inflammatory medication (like Advil or Motrin) an hour before the procedure.

If an adequate amount of tissue was not obtained by the endometrial biopsy, or if the biopsy tissue looks abnormal but confirmation is needed, the doctor may perform a **dilatation and curettage** (D & C). This procedure is done in the outpatient surgery department of a hospital and takes about an hour. The patient may be given general anesthesia. The doctor dilates the cervix and uses a special instrument to scrape tissue from inside the uterus.

The tissue that is obtained from the biopsy or the D & C is sent to a laboratory for examination. If cancer is found, then the type of cancer will be determined. The treatment and prognosis depends on the type and stage of the cancer.

Transvaginal ultrasound may be used to measure the thickness of the endometrium. For this painless procedure, a wand-like ultrasound transducer is inserted into the vagina to enable visualization and measurement of the uterus, the thickness of the uterine lining, and other pelvic organs.

Other possible diagnostic procedures include sonohysterography and hysteroscopy. For sonohysteroscopy, a small tube is passed through the cervix and into the uterus. A small amount of a salt water (saline) solution is injected through the tube to open the space within the uterus and allow ultrasound visualization of the endometrium. For hysteroscopy, a wand-like camera is passed through the cervix to allow direct visualization of the endometrium. Both of these procedures cause discomfort, which may be reduced by taking an anti-inflammatory medication prior to the procedure.

Colored scanning electron micrograph of adenocarcinoma cancer in the endometrium, the lining of the uterus. Here, surface epithelial cells are seen (yellow), with cavities forming the openings of glands. Adenocarcinoma cells are large (green) and proliferative, invading the surface and glands. *(Copyright Professors P.M. Motta and S. Makabe, Science Source/ Photo Researchers, Inc. Photo reproduced by permission.)*

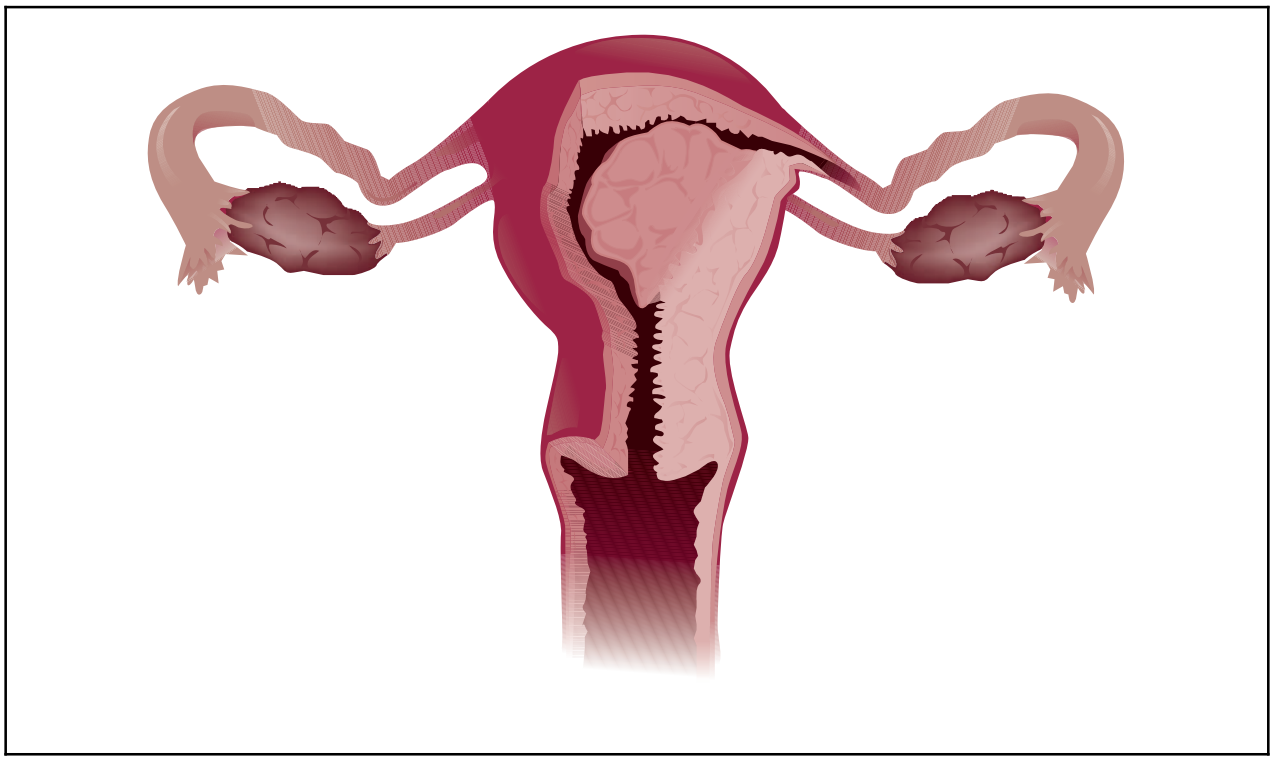
Treatment team

The treatment team for endometrial cancer may include a gynecologist, gynecologic oncologist, surgeon, radiation oncologist, gynecologic nurse oncologist, sexual therapist, psychiatrist, psychological counselor, and social worker.

Clinical staging, treatments, and prognosis

Clinical staging

The International Federation of Gynecology and Obstetrics (FIGO) has adopted a staging system for



Cancer located in the uterus. *(Illustration by Argosy Publishing Inc. Reproduced by permission of The Gale Group.)*

endometrial cancer. The stage of cancer is determined after surgery. Endometrial cancer is categorized into four stages (I, II, III, and IV) which are subdivided (A, B, and possibly C) based on the depth or spread of cancerous tissue. Seventy percent of all uterine cancers are stage I, 10% to 15% are stage II, and the remainder are stages III and IV. The cancer is also graded (G1, G2, and G3) based upon microscopic analysis of the aggressiveness of the cancer cells.

The FIGO stages for endometrial cancer are:

- Stage I. Cancer is limited to the uterus.
- Stage II. Cancer involves the uterus and cervix.
- Stage III. Cancer has spread out of the uterus but is restricted to the pelvic region.
- Stage IV. Cancer has spread to the bladder, bowel, or other distant locations.

Treatments

The mainstay of treatment for most stages of endometrial cancer is surgery. **Radiation therapy**, hormonal therapy, and **chemotherapy** are additional treatments (called adjuvant therapy). The necessity of adjuvant therapy is a controversial topic which should be discussed with the patient's treatment team.

SURGERY Most women with endometrial cancer, except those with stage IV disease, are treated with hysterectomy. A simple hysterectomy involves the removal of the uterus. In a bilateral salpingo-oophorectomy with total hysterectomy, the ovaries, fallopian tubes, and uterus are removed. This may be necessary because endometrial cancer often spreads to the ovaries first. The lymph nodes in the pelvic region may also be biopsied or removed to check for **metastasis**. Hysterectomy is traditionally performed through an incision in the abdomen (laparotomy), however, endoscopic surgery (**laparoscopy**) with vaginal hysterectomy is also being used. Women with stage I disease may require no further treatment. However, those with higher grade disease will receive adjuvant therapy.

RADIATION THERAPY The decision to use radiation therapy depends on the stage of the disease. Radiation therapy may be used before surgery (preoperatively) and/or after surgery (postoperatively). Radiation given from a machine that is outside the body is called external radiation therapy. Sometimes applicators containing radioactive compounds are placed inside the vagina or uterus. This is called internal radiation therapy or brachytherapy and requires hospitalization.

Side effects are common with radiation therapy. The skin in the treated area may become red and dry.

Fatigue, upset stomach, **diarrhea**, and nausea are also common complaints. Radiation therapy in the pelvic area may cause the vagina to become narrow (vaginal stenosis), making intercourse painful. Premature menopause and some problems with urination may also occur.

CHEMOTHERAPY Chemotherapy is usually reserved for women with stage IV or recurrent disease because this therapy is not a very effective treatment for endometrial cancer. The anticancer drugs are given by mouth or intravenously. Side effects include stomach upset, vomiting, appetite loss (anorexia), hair loss (alopecia), mouth or vaginal sores, fatigue, menstrual cycle changes, and premature menopause. There is also an increased chance of infections.

HORMONAL THERAPY Hormonal therapy uses drugs like progesterone to slow the growth of endometrial cells. These drugs are usually available as pills. This therapy is usually reserved for women with advanced or recurrent disease. Side effects include fatigue, fluid retention, and appetite and weight changes.

Prognosis

Because it is possible to detect endometrial cancer early, the chances of curing it are excellent. The five year survival rates for endometrial cancer by stage are: 90%, stage I; 60%, stage II; 40%, stage III; and 5%, stage IV. Endometrial cancer most often spreads to the lungs, liver, bones, brain, vagina, and certain lymph nodes.

Alternative and complementary therapies

Although alternative and complementary therapies are used by many cancer patients, very few controlled studies on the effectiveness of such therapies exist. Mind-body techniques such as prayer, biofeedback, visualization, meditation, and yoga, have not shown any effect in reducing cancer but they can reduce stress and lessen some of the side effects of cancer treatments. Clinical studies of hydrazine sulfate found that it had no effect on cancer and even worsened the health and well- being of the study subjects. One clinical study of the drug amygdalin (Laetrile) found that it had no effect on cancer. Laetrile can be toxic and has caused deaths. Shark cartilage, although highly touted as an effective cancer treatment, is an improbable therapy that has not been the subject of clinical study.

The American Cancer Society has found that the "metabolic diets" pose serious risk to the patient. The effectiveness of the macrobiotic, Gerson, and Kelley diets and the Manner metabolic therapy has not been scientifically proven. The FDA was unable to substantiate the anticancer claims made about the popular Cancell treatment.

There is no evidence for the effectiveness of most over-the-counter herbal cancer remedies. Some herbals have shown an anticancer effect. As shown in clinical studies, Polysaccharide krestin, from the mushroom *Coriolus versicolor*, has significant effectiveness against cancer. In a small study, the green alga *Chlorella pyrenoidosa* has been shown to have anticancer activity. In a few small studies, evening primrose oil has shown some benefit in the treatment of cancer.

KEY TERMS

Adjuvant therapy—A treatment done when there is no evidence of residual cancer in order to aid the primary treatment. Adjuvant treatments for endometrial cancer are radiation therapy, chemotherapy, and hormone therapy.

Atypical adenomatous hyperplasia—The overgrowth of the endometrium. This precancerous condition is estimated to progress to cancer in one third of the cases.

Dilation and curettage (D & C)—A procedure in which the doctor opens the cervix and uses a special instrument to scrape tissue from the inside of the uterus.

Endometrial biopsy—A procedure in which a sample of the endometrium is removed and examined under a microscope.

Endometrium—The mucosal layer lining the inner cavity of the uterus. The endometrium's structure changes with age and with the menstrual cycle.

Estrogen—A female hormone responsible for stimulating the development and maintenance of female secondary sexual characteristics.

Estrogen replacement therapy (ERT)—A treatment in which estrogen is used therapeutically during menopause to alleviate certain symptoms such as hot flashes. ERT has also been shown to reduce the risk of osteoporosis and heart disease in women.

Progesterone—A female hormone that acts on the inner lining of the uterus and prepares it for implantation of the fertilized egg.

Progestins—A female hormone, like progesterone, that acts on the inner lining of the uterus.

QUESTIONS TO ASK THE DOCTOR

- What type of cancer do I have?
- What stage of cancer do I have?
- What is the five-year survival rate for women with this type of cancer?
- Has the cancer spread? What tests will be used to determine this?
- What are my treatment options?
- Is adjuvant therapy really necessary in my case?
- What are the risks and side effects of these treatments?
- What medications can I take to relieve treatment side effects?
- Are there any clinical studies underway that would be appropriate for me?
- What effective alternative or complementary treatments are available for this type of cancer?
- How debilitating is the treatment? Will I be able to continue working?
- How will the treatment affect my sexuality?
- Are there any restrictions regarding sexual activity?
- Are there any local support groups for endometrial cancer patients?
- What is the chance that the cancer will recur?
- Is there anything I can do to prevent recurrence?
- How often will I have follow-up examinations?

For more comprehensive information, the patient should consult the book on complementary and alternative medicine published by the American Cancer Society listed in the Resources section.

Coping with cancer treatment

The patient should consult her treatment team regarding any side effects or complications of treatment. Vaginal stenosis can be prevented and treated by vaginal dilators, gentle douching, and sexual intercourse. A water-soluble lubricant may be used to make sexual intercourse more comfortable. Many of the side effects of chemotherapy can be relieved by medications. Women should consult a psychotherapist and/or join a support group to deal with the emotional consequences of cancer and hysterectomy.

Clinical trials

Because endometrial cancer is a common type of cancer there are many studies underway to optimize its treatment. Women should consult with their treatment team to determine if they are candidates for any ongoing studies.

Prevention

Women (especially postmenopausal women) should report any abnormal vaginal bleeding or discharge to the doctor. Controlling obesity, blood pressure, and diabetes can help to reduce the risk of this disease. Women on estrogen replacement therapy have a substantially reduced risk of endometrial cancer if progestins are taken simultaneously. Long-term use of birth control pills has been shown to reduce the risk of this cancer. Women who have irregular periods may be prescribed birth control pills to help prevent endometrial cancer. Women who are taking tamoxifen and those who carry the hereditary nonpolyposis colorectal cancer gene should be screened regularly, receiving annual pelvic examinations.

Special concerns

Of special concern to the young woman with endometrial cancer is the impact that a hysterectomy will have on her fertility, **sexuality**, and **body image**. **Depression** is common. Symptoms caused by the sudden onset of menopause, due to removal of the ovaries, can be more severe than with natural menopause. Estrogen replacement therapy is not commonly used due to the potential risk of cancer recurrence. Without estrogen replacement, osteoporosis becomes a concern and calcium supplements should be considered. Weight bearing exercise and alendronate (Fosamax) will also decrease the development rate of osteoporosis. Vaginal stenosis following radiation treatment is a concern.

Resources

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American Cancer Society, National Headquarters. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) 227-2345. <http://www.cancer.org/>.

Cancer Research Institute, National Headquarters. 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

Gynecologic Cancer Foundation. 401 North Michigan Ave., Chicago, IL 60611. (800) 444-4441. <http://www.wcn.org>.

National Cancer Institute, National Institutes of Health. 9000 Rockville Pike, Bethesda, MD 20892. (800) 422-6237. <http://cancernet.nci.nih.gov/>.

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Belinda Rowland, Ph.D.

Endorectal ultrasound

Definition

Ultrasound is a type of imaging technique that painlessly uses sound waves to produce an image of internal structures, organs, and masses. Endorectal ultrasound, also called transrectal ultrasound, is a special ultrasound technique in which the transducer is directly inserted through the anus and into the patient's rectum. The sound wave echoes detected by the transducer are converted by a computer into an image.

Purpose

Ultrasound technology has been used in medicine since World War II and is recognized as a non-invasive, non-radiative, real-time and inexpensive imaging capacity. It has become standard medical practice to produce fetal images and to identify and assess various anatomical features of the body.

Endorectal ultrasound is a specialized ultrasound application and it represents one of the most useful diagnostic tools for diseases of the anal and rectal regions of the body, especially for rectal, anal, and prostrate cancer screening and staging.

For **rectal cancer**, endorectal ultrasound is the most preferred method for staging both depth of tumor penetration and local lymph node metastatic status. Endorectal ultrasound:

- differentiates areas of invasion within large rectal adenomas that seem benign
- determines the depth of tumor penetration into the rectal wall
- determines the extent of regional lymph node invasion
- can be combined with other tests (chest x rays and **computed tomography** scans, or CT scans) to determine the extent of cancer spread to distant organs, such as the lungs or liver The resulting rectal cancer staging allows physicians to determine the need for— and order of— radiation, surgery, and **chemotherapy**.

For patients diagnosed with **anal cancer**, endorectal ultrasound may help to stage the lesion and may be used as follow-up care to check for recurrence of cancer after treatment.

In the diagnosis of prostrate cancer, endorectal ultrasound has become a companion technique to **digital rectal examination** (DRE). It is also the most frequent method used to guide **biopsy** needle insertion. If surgery is indicated, endorectal ultrasound can also assist the preoperative evaluation of the depth of cancer penetration and of the presence of metastases, as required to design appropriate surgical procedures.

Endorectal ultrasounds can also be used to check the overall treatment results.

Precautions

This is a very easy procedure. Unlike other imaging techniques, it uses no radiation and thus requires no special precautions.

KEY TERMS

Anal—Pertaining to the anus, which is the terminal orifice of the digestive—or alimentary—canal.

Anatomy—Structure of the body and of the relationship between its parts.

Biopsy—Procedure that involves obtaining a tissue specimen for microscope analysis to establish a precise diagnosis.

Cancer screening—Examination of people to detect early stages in the development of cancer even though they have no symptoms.

Colon—Large intestine.

Digital rectal examination (DRE)—Examination performed by a physician to detect rectal cancer. The physician inserts a gloved, lubricated finger into the rectum of the patient and feels for abnormal areas.

Endorectal probe—Instrument which sends sound waves through the prostrate. Sound echoes are then recorded as an image.

Enema—Injection of a liquid into the rectum.

Metastasis—The transfer of cancer from one part of the body to another not directly connected with it.

Rectal—Pertaining to the rectum, which is the last portion of the large intestine.

Sonogram —A computer picture of areas inside the body created by bouncing sound waves off organs and other tissues. Also called ultrasonogram or ultrasound.

Description

The instrumentation used for endorectal ultrasound consists of a hand-held probe, the transrectal transducer, a scanner, and an imaging screen. During the procedure, high-frequency acoustical (sound) waves are sent out by the small microphone-like transducer, which is inserted into the rectum. The waves bounce off the organ being examined and produce echoes sent by the transducer to a computer so as to generate a picture called a sonogram. Doctors examine the sonogram for echoes that may represent abnormal areas.

Usually, the patient lies on his side during the test. An endorectal probe is covered with a protective covering and inserted into the patient. The probe looks like a small enema tip and there is a minimal amount of discomfort associated with the procedure itself. Once inserted, the sonographer or radiologist gently moves the probe forward and backward to best evaluate the organ being examined. An endorectal ultrasound generally takes five to ten minutes. After the procedure, the radiologist interprets the results and sends a report to the referring physician.

Preparation

The patient requires no anesthetic or sedation, but needs an enema about two hours before the test in order to provide a clean rectal wall through which to scan. The evening before the procedure, it is recommended that the patient eat a small dinner, drinking only clear liquids and avoiding coffee, tea, or soft drinks after dinner.

Aftercare

The patient should enjoy a good meal and remember to keep a follow-up appointment if scheduled. In some cases, there may be some bleeding from the rectum, though this usually settles within a few days. **Antibiotics** may be prescribed in some cases.

Risks

Multiple studies have shown that the sound waves used with ultrasound imaging are harmless and may be directed at patients with complete safety. However, some patients may develop infections following the procedure, which could require further treatment. These may cause shivering and **fever**. Any manifestation of such symptoms should be immediately reported to the treating physician. Generally speaking, the entire procedure is well tolerated and there is usually minimal bleeding afterwards.

Normal results

Normal sonograms produce images that have the correct shape of the organ or tissue examined by the procedure, meaning that it corresponds to the true anatomy.

Abnormal results

Abnormal sonograms produce images which highlight abnormal features of the organ being scanned. In a tumor is present, it will show up as a distinct contrast feature on the sonogram.

See also Imaging studies.

Resources

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QUESTIONS TO ASK THE DOCTOR

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- Are any other imaging tests indicated?
- How will this test help you diagnose my cancer?

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Endoscopic retrograde cholangiopancreatography

Definition

Endoscopic retrograde cholangiopancreatography (ERCP) is a technique in which a hollow tube called an endoscope is passed through the mouth and stomach to the duodenum (the first part of the small intestine). This procedure was developed to examine abnormalities of the bile ducts, pancreas, and gallbladder. It was developed during the late 1960s and is used today to diagnose and treat blockages of the bile and pancreatic ducts.

The term has three parts to its definition:

- "Endoscopic" refers to the use of an endoscope.
- "Retrograde" refers to the injection of dye up into the bile ducts in a direction opposing, or against, the normal flow of bile down the ducts.
- Cholangiopancreatography means visualization of the bile ducts (cholangio) and pancreas (pancreato).

Purpose

Until the 1970s, methods to visualize the bile ducts produced images that were of relatively poor quality and often misleading; in addition, the pancreatic duct could not be examined at all. Patients with symptoms related to the bile ducts or pancreatic ducts frequently needed surgery to diagnose and treat their conditions.

Using ERCP, physicians can obtain high-quality x rays of these structures and identify areas of narrowing (strictures), cancers, and gallstones. This procedure can help determine whether bile or pancreatic ducts are blocked; it also identifies where they are blocked along with the cause of the blockage. ERCP may then be used to relieve the blockage. For patients requiring surgery or additional procedures for treatment, ERCP outlines the anatomical changes for the surgeon.

Precautions

The most important precaution is that the examination should be performed by an experienced physician. The procedure is much more technically difficult than many other gastrointestinal endoscopic studies. Patients should seek physicians with experience performing ERCP. Patients should inform the physician about any allergies (including allergies to contrast dyes, iodine, or shellfish), medication use, and medical problems. Occasionally, patients may need to be admitted to the hospital after the procedure.

Description

After sedation, a specially adapted endoscope is passed through the mouth, through the stomach, then into the duodenum. The opening to ducts that empty from the liver and pancreas is identified, and a plastic tube or catheter is placed into the orifice (opening). Contrast dye is then injected into the ducts, and with the assistance of a radiologist, pictures are taken.

KEY TERMS

Endoscope, endoscopy—An endoscope used in the field of gastroenterology is a hollow, thin, flexible tube that uses a lens or miniature camera to view various areas of the gastrointestinal tract. When the procedure is performed to examine the bile ducts or pancreas, the organs are not viewed directly, but rather indirectly through the injection of contrast. The performance of an exam using an endoscope is referred to as endoscopy. Diagnosis through biopsies or other means and therapeutic procedures can also be done using these instruments.

Visualization—The process of making an internal organ visible. A radiopaque substance is introduced into the body, then an x-ray picture of the desired area is taken.

QUESTIONS TO ASK THE DOCTOR

- How soon will you know the results?
- Did you see any abnormalities?
- When can I resume any medications that were stopped?
- When can I resume normal activities?
- What future care will I need?

Preparation

The upper intestinal tract must be empty for the procedure, so patients should NOT eat or drink for at least 6 to 12 hours before the exam. Patients should ask the physician about taking their medications before the procedure.

Aftercare

Someone should be available to take the person home after the procedure and stay with them for a while; patients will not be able to drive themselves because they undergo sedation during this test. Pain or any other unusual symptoms should be reported to the physician.

Risks

ERCP-related complications can be broken down into those related to medications used during the procedure, the diagnostic part of the procedure, and those related to endoscopic therapy. The overall complication rate is 5% to 10%; most of those occur when diagnostic ERCP is combined with a therapeutic procedure. During the exam, the endoscopist can cut or stretch structures (such as the muscle leading to the bile duct) to treat the cause of the patient's symptoms. Although the use of sedatives carries a risk of decreasing cardiac and respiratory function, it is very difficult to perform these procedures without these drugs.

The major complications related to diagnostic ERCP are pancreatitis (inflammation of the pancreas) and cholangitis (inflammation of the bile ducts). Bacteremia (the passage of bacteria into the blood stream) and perforation (hole in the intestinal tract) are additional risks.

Normal results

Because certain standards have been set for the normal diameter or width of the pancreatic duct and bile ducts, measurements using x rays are taken to determine if the ducts are too large (dilated) or too narrow (strictured). The ducts and gallbladder should be free of stones or tumors.

Abnormal results

When areas in the pancreatic or bile ducts (including those in the liver) are too wide or too narrow compared with the standard, the test is considered abnormal. Once these findings are demonstrated using ERCP, symptoms are usually present; they generally do not change without treatment. Stones, identified as opaque or solid structures within the ducts, are also considered abnormal. Masses or tumors may also be seen, but sometimes the diagnosis is made not by direct visualization of the tumor, but by indirect signs, such as a single narrowing of one of the ducts. Overall, ERCP has an excellent record in diagnosing these abnormalities.

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Endoscopic ultrasound *see* **Ultrasonography**

Enoxaparin *see* **Low molecular weight Heparin**

Enteritis

Description

Enteritis is an inflammation of the intestine; the term applies chiefly to the small intestine. In the context of cancer, enteritis is a functional disorder of the large and small bowel that occurs as a result of **radiation therapy** applied to the abdomen, pelvis, or rectum. It occurs at the onset of radiation therapy (acute radiation enteritis) and may also reappear after completion of the radiation treatment (chronic enteritis).

Enteritis also occurs in connection with such disorders as Crohn's disease and infection by such pathogens as *Helicobacter pylori*. Patients who receive hemodialysis for kidney disorders as well as cancer patients have an increased risk of enteritis.

Causes

Radiation enteritis occurs because the large and small intestines are sensitive to all forms of ionizing radiation. Some areas of the gastrointestinal tract are more sensitive to radiation than others; the colon is more sensitive to the effects of radiation than the small intestine, for example. Although the probability of tumor control increases with the radiation therapy dose, so does the probability of damage to normal healthy tissues. Since the doses required to destroy many tumors are very high, acute side effects to the intestines also occur, chief among which is enteritis. Thus, the majority of patients undergoing radiation to the abdomen, pelvis, or rectum will show signs of acute enteritis.

Symptoms of the disorder are observed during the first course of radiation treatment and take about eight weeks to become acute. Chronic radiation enteritis may also occur months to years after a patient has undergone a course of radiation therapy. The symptoms include colicky abdominal pain, bloody **diarrhea**, tenesmus, **weight loss**, **nausea and vomiting**, bowel obstruction and rectal bleeding, sometimes very severe.

Several factors influencing the occurrence and extent of radiation enteritis have been identified. They include the dose of radiation given to the patient, the size of the tumor being treated, the concomitant prescription of **chemotherapy** and the general state of the patient's health. For example, enteritis will be more severe in patients with a history of hypertension, diabetes or inadequate nutrition.

Treatments

Some symptoms of radiation enteritis are caused by an overgrowth of bacteria. In these cases, **antibiotics** may be prescribed. Patients who develop acute enteritis report nausea, vomiting, abdominal cramping, and diarrhea. Diarrhea impairs the digestive and absorptive functions of the gastrointestinal tract, resulting in malabsorption of fat, lactose, bile salts, and vitamin B12. Patients also complain about rectal pain and bleeding. Treatment of acute enteritis accordingly includes treating diarrhea, dehydration and abdominal and rectal pain or discomfort. Antidiarrheal drugs are usually prescribed, such as Kaopectate, Lomotil, Paregoric or Imodium. Additionally, bile salt–retaining drugs may also be indicated, such as cholestyramine. Bowel cramps may be alleviated with antispamodic drugs, such as Donnatal.

Some patients with radiation enteritis can be fed through a tube leading into the stomach provided the small intestine is functioning normally. Otherwise, they may require parenteral alimentation, which means that a nutrient solution is given intravenously.

Approximately 5%–10% of patients having received radiation therapy for abdominal or pelvic cancers develop chronic enteritis. In some cases, surgery may be indicated. There is at present no agreement as to the proper timing and choice of surgical intervention in such cases. Surgery is thus only undertaken after careful assessment of individual patient conditions and health status.

Surgery may also be indicated for patients who have developed radiation enteritis–induced strictures. (Strictures are narrowing of passages or canals.)

Alternative and complementary therapies

An important complementary therapy is nutrition management. Another side effect of radiation is to destroy the intestinal villi, which impairs the body's capacity to absorb nutrients and also destroys enzymes required for digestion, such as lactase, required to digest milk and dairy products. Thus a lactose-free diet is often recommended.

Besides milk and dairy products, it is often recommended to avoid foods such as whole bran bread and cereals, nuts, seeds and coconuts, fried and greasy foods, fruit and some fruit juices (prune juice especially),

KEY TERMS

Acute—Medical condition which has a short and relatively severe course.

Chronic—Medical condition persisting over a long period of time.

Gastrointestinal tract—The gastrointestinal tract starts with the oral cavity (mouth) and proceeds to the esophagus, the stomach, the duodenum, the small intestine, the large intestine, the rectum and the anus.

Intestinal villi—Microscopic finger-like projections located on the lining of the small intestine which are responsible for the absorption of nutrients.

Ionizing radiation—Radiation sufficiently energetic so as to remove electrons from an atom. Examples are x rays, gamma rays, beta radiation (electrons) and alpha radiation (helium nuclei) as well as the radiation emitted by heavier elements. The higher the energy of ionizing radiation, the more likely the tissue or cell damage.

Lactose—The major sugar present in human and bovine milk.

Parenteral alimentation—A form of feeding in which the patient is given nutrients in a solution intravenously.

Tenesmus—Painful straining to pass stool or urine.

uncooked vegetables, potato chips, pretzels, strong spices and herbs, chocolate, coffee, tea, alcohol and tobacco.

Recommended foods include fish, poultry, and cooked, broiled, or roasted meat, bananas, apple sauce, peeled apples, apple and grape juices, white bread, noodles, baked, boiled, or mashed potatoes, cooked vegetables such as asparagus tips, green and waxed beans, carrots, spinach, mild processed cheese, eggs, smooth peanut butter, buttermilk, yogurt and nutmeg.

Additionally, patients with radiation enteritis may be helped by eating their food at room temperature and by drinking plenty of water every day. Carbonated sodas should be allowed to lose their carbonation prior to drinking.

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Environmental factors in cancer development

Definition

Environment as a cause of cancer is a complex and often misunderstood topic. The term environment has several different meanings when referring to causation of cancer. Originally, the term "environmental cause of cancer" was used to refer to all cancers that were not caused by hereditary or inherited factors. This definition included all cancers caused by lifestyle practices such as diet and tobacco use, viruses, and many other causes. For purposes of clarification, the term "environment" has been further defined by adding the labels "personal environment" and "external environment" when referring to causes of cancer.

By this definition, causes of cancer related to an individual's personal environment includes lifestyle choices such as diet, use of tobacco, and other factors that may place the individual at high risk for the development of cancer. External environmental causes of cancer refer to factors in the environment such as environmental pollutants that increase risk for cancer. Up to 85% of cancer is due to lifestyle choices made by individuals, which places them at higher risk for the development of cancer. For example, tobacco is directly related to more than 30% of cancer deaths. Considering more than 500,000 deaths per year are caused by tobacco alone,

risk for cancer development due to external environmental factors pales in comparison.

Epidemiologists are scientists who research and identify factors that are common to cancer patients' histories and lifestyles, and then evaluate those factors within the context of current biological and disease causation theories. Eventually, evidence may persuade epidemiologists to conclude that one or more factors or characteristics shared by a study group "caused" a disease such as a type of cancer. The science of epidemiology enables researchers to determine causes of diseases such as specific types of cancer, and also to estimate or project numbers of deaths that can be attributed to the cause on an annual basis.

Personal environment/Lifestyle choices

Tobacco use

Tobacco is known as one of the most potent carcinogens in humans. Tobacco causes more than 148,000 deaths each year in the form of various cancers such as lung, trachea, bronchus, larynx, pharynx, oral cavity, and esophagus. Other cancers linked to tobacco use include cancers of the pancreas, kidney, bladder, and cervix. Smoking's effects on cancer continue to be shown. New research in 2004 linked a mother's smoking to increased risk of testicular cancer in their children. Cigarette smoking is more common among men; however, because of the increase in the number of women who smoke, more women die from lung cancer each year than from **breast cancer**. The life span of an individual who smokes is shortened by an average of 12 years.

Diet and nutrition

According to the American Cancer Society, the single most important dietary intervention to lower risk for cancer is eating five or more servings of fruits and vegetables daily. Consuming a diet rich in plant sources provides phytochemicals—non-nutritive substances in plants that possess health protective benefits. A diet rich in foods from plant sources reduces the risk for development of cancers of the gastrointestinal tract, respiratory tract, and colon. Increased consumption of fruits and vegetables is also associated with decreased risk for lung cancer.

Diets high in fat have been associated with increased risk for colon, rectal, prostate, and endometrial cancers. The association between high-fat diets and the development of breast cancer is much weaker. Specific recommendations are to replace high-fat foods with fruits and vegetables, eat smaller portions of high-fat foods, and limit consumption of meats—especially those that are considered high fat. Foods from animal sources remain a staple in American diets. Consumption of meat, especially red meats such as beef, pork, and lamb, have been associated with increased risk of colon and **prostate cancer**.

Obesity is often the result of meat-based, high-fat diets. Obesity has been linked to cancers at several sites including colon and rectum, prostate, kidney, and endometrium. Weight gain in early adulthood seems to increase risk for breast cancer, especially if the gain occurred in the third decade of life. The highest risk related to obesity and the development of breast cancer is in postmenopausal women.

Alcohol use

Drinking alcohol increases the risk of developing cancers of the mouth, esophagus, pharynx, larynx, and liver in men and women; and increases the risk of breast cancer in women. Cancer risk increases as the amount of alcohol consumed increases. An individual who both smokes and drinks alcohol greatly increases the risk of developing cancer when compared to either smoking or drinking alone.

Physical activity

Recommendations related to physical exercise have included engaging in moderate levels of activity for at least 30 minutes on most days of the week. Many physicians have encouraged even more exercise to decrease obesity and increase overall health. Studies have revealed an association between physical activity and a reduced risk of the development of certain types of cancers, including colon, breast, and prostate cancer.

Radiation exposure

Only high frequency radiation such as ultraviolet (UV) radiation and ionizing radiation (IR) has been proven to cause cancer in humans. A source of UV radiation is sunlight. Prolonged exposure to UV radiation is the major cause of basal and squamous cell skin cancers. UV radiation is also a major cause of **melanoma**.

IR has cancer-causing capability, as proven by studies on atomic bomb survivors and other groups. Virtually any part of the body can by affected by IR, but the areas most affected are the bone marrow and the thyroid gland. IR is released in very low levels from diagnostic equipment such as medical and dental X-ray equipment. Much higher levels of IR are released from machines delivering **radiation therapy** to patients. Great precautions are taken not to expose patients or staff unnecessarily to the effects of IR.

Exposure to radon, a form of IR, can increase risk for lung cancer, especially among smokers. Radon is a naturally occurring radioactive gas formed by the decay of uranium in rocks and soil. The gas is odorless, colorless, tasteless, and cannot be detected by sight. Radon seeps up through the ground and is released into the air. Radon gas exists at harmless levels outdoors. In areas where there is poor ventilation, such as underground mines, radon can accumulate to levels that pose a risk for the development of lung cancer. Radon causes cancer by emitting radioactive particles as it decays. These particles damage the lining of the lung when the radon is inhaled. Individuals at highest risk for the development of cancer from radon exposure include uranium miners and those individuals who live in well-insulated, tightly sealed homes built on uranium-rich soil. Testing for radon is the only way to determine if a home has elevated radon levels.

Reproductive and gynecologic factors

Lifestyle choices linked to breast cancer include diet, **alcohol consumption**, oral contraceptives, estrogen replacement therapy, postmenopausal obesity, and nulliparity (a woman who has never had a child). The relationship between dietary fats and breast cancer continues to be studied. Women who consume more than two alcoholic drinks per day are at higher risk. Oral contraceptive use has been linked to the development of breast cancer. Nulliparous women who began using oral contraceptives prior to the age of 18 years and continued uninterrupted use for more than eight years have a minimally increased risk. In 2002, a large study of hormone replacement therapy for postmenopausal women was halted because of the large risk of breast cancer (and heart disease) the therapy produced in women. In early 2004, researchers also found increased risk of breast cancer recurrence in women who used the hormone therapy for postmenopausal symptoms.

Full-term pregnancy seems to exert a deterrent effect on the development of breast cancer. Women who become pregnant after the age of 30 years, or who never become pregnant, are at higher risk. Historically, lactation and breast-feeding have been recognized as protective mechanisms for breast cancer development. A correlation between the development of breast cancer and abortion has been documented in United States studies. A large study conducted in Denmark to investigate the correlation found no increased risk of breast cancer among women who had undergone abortions.

Precancerous and cancerous lesions of the cervix are associated with many personal risk factors, including a higher incidence in women who become sexually active prior to age 17, have many sex partners, and are multiparous (have borne at least one living child). An association has also been described between type of employment and increased **cervical cancer** mortality. Women with higher mortality rates include women once employed in farm work, manufacturing, personal services, or who worked as nurses' aides. Women who are infected with the human immunodeficiency virus (HIV) are at higher risk for the development of squamous intraepithelial lesions of the cervix. Cervical cancer is not often diagnosed in women who are nulliparous, those who are lifetime celibates, or who are lifetime monogamous (having sex with only one person).

Psychological stress

Stress is known to activate the body's endocrine or hormonal system which in turn causes changes in the immune system. There is no specific evidence that changes in the immune system caused by stress directly cause cancer. However, some studies report significantly higher rates of breast cancer in women who experienced stressful life events and losses in the years immediately preceding the diagnosis of breast cancer. Other studies do not support the association between stress and breast cancer development.

Cellular phone use

Studies in the United States and Denmark in 2000 and 2001 revealed there is no link between cellular telephone use and tumors of the brain, salivary gland, leukemia, or other cancers. The type of telephone, the duration of the cell phone use, or age of the phone user had no effect on cancer risk.

External environment

Chemicals and other substances

Exposure to certain chemicals, pesticides, and metals can increase an individual's risk for cancer. Carcinogens in this category include nickel, cadmium, vinyl chloride, and benzene. These carcinogens may act alone or in combination with another carcinogen, such as cigarette smoke, to increase risk for cancer.

Environmental tobacco smoke (secondhand smoke)

Environmental tobacco smoke (ETS) is a combination of two forms of smoke from tobacco products—sidestream smoke and mainstream smoke. Sidestream smoke is smoke released between puffs of a burning cigarette, cigar, or pipe. Mainstream smoke is the smoke that is exhaled by the smoker. Sidestream smoke contains essentially the same compounds as those in the

mainstream smoke inhaled by the smoker. Tobacco smoke is known to contain at least 60 different carcinogens. Nonsmokers who are exposed to ETS absorb nicotine and other harmful compounds from the smoke. ETS can cause lung cancer in healthy adults who are nonsmokers and there is a 20% increased risk of lung cancer in nonsmokers exposed to ETS. ETS has been linked to other cancers, including cancers of the nasal cavity, cervix, breast, and bladder. In 1992, the U.S. Environmental Protection Agency classified ETS as a Group A carcinogen. Group A is reserved by the EPA to categorize only the most dangerous cancer-causing agents to humans.

Asbestos exposure

Asbestos is a group of minerals that occur naturally as strong, flexible fibers that can be separated into threads and then woven. Asbestos fibers cannot conduct electricity and are not affected by heat or chemicals. Because of these properties there have been many industrial applications of asbestos. Some of the applications include insulation, fireproofing, and absorption of sound. Serious health risks related to asbestos occur as a result of exposure to the dust that is formed when the fibers break into tiny particles. These asbestos particles can then be inhaled or swallowed. Exposure to asbestos can lead to lung, larynx, and gastrointestinal tract cancers, as well as to the rare cancer—mesothelioma. Individuals at highest risk include those with the combination of asbestos exposure and smoking. Smoking increases risk for lung cancer by 10 times more than for the nonsmoker also exposed to asbestos. Due to government regulations and public concerns about the health hazards from asbestos exposure, the use of asbestos in the United States has declined significantly. Workplace practices involving asbestos are highly regulated by industry and government to minimize worker exposure.

Electric and magnetic field (EMF) exposure

EMFs are emitted from devices that produce, transmit, or use electric power and arise from the motion of electrical charges. Examples of these devices include power lines, transmitters, and household products such as microwave ovens, electric blankets, televisions, and computers. EMFs are considered forms of nonionizing radiation. According to the National Cancer Institute (NCI), public concern has increased over the health effects of EMFs, particularly in relation to the risk of developing cancer in both children and adults exposed to EMFs. Numerous studies have been conducted in the past 15 years to evaluate risk of cancer from exposure to EMFs. As of 2001, the results have been inconsistent according to the NCI. One large NCI/Children's Cancer Group study sought to determine whether exposure to magnetic fields contributed to the development of acute lymphoblastic leukemia (ALL) in children under the age of 15 years. The results of this study revealed little evidence of a relationship between risk for ALL in children and exposure to magnetic fields.

Other studies focused on determining links between magnetic fields and central nervous system (CNS) tumors such as brain cancers continue to be actively researched. To date, expert panels that have reviewed the existing data have concluded that data are insufficient to support the conclusion that magnetic fields cause cancer.

Nuclear facility exposure

An NCI study published in 1991 concluded there was no general increased risk of death from cancer for people living in more than 100 U.S. counties containing, or closely adjacent to, nuclear facilities. A British survey of cancer mortality in areas around nuclear facilities in the United Kingdom reported an increase in deaths from childhood leukemia near some of the facilities. Other smaller surveys of cancer deaths around nuclear facilities in both countries yielded conflicting results.

See also Cigarettes; Occupational exposures and cancer; Cancer prevention.

KEY TERMS

Carcinogen—A cancer-causing agent.

Lactation—The process of synthesis and secretion of milk from the breasts for nourishment of an infant or child.

Mulitparous—A woman who has given birth to at least one child.

Nulliparous—A woman who has not given birth to a living infant.

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Ependymoma

Definition

An ependymoma is a rare type of primary brain tumor that develops from the ependymal cells lining the ventricles of the brain and the central canal of the spinal cord. Ependymomas can be found anywhere in the brain or spine but are usually located in the main part of the brain, the cerebrum, and may spread from the brain to the spinal cord via the cerebrospinal fluid (CSF).

Description

Most brain tumors are named after the cells in which they are found, thus the name ependymoma for a tumor of ependymal cells. Ependymomas are classified as either supratentorial (located in the top part of the head) or infratentorial (located in the back of the head). In children, most ependymomas are of the infratentorial type and occur in or close to the fourth ventricle of the brain. Ependymomas may block the flow of cerebrospinal fluid out of the ventricles causing them to enlarge—a condition called hydrocephalus. Unlike other types of brain tumors, ependymomas as a rule do not spread into healthy brain tissue or outside the brain or spinal cord. As a result, it is often the case that they can be removed and cured by surgery, especially spinal cord ependymomas.

Demographics

Ependymomas are infrequent tumors, representing 2% to 8% of all brain tumors. However, ependymomas are the third most common brain tumor in childhood (5% to 10%) and are diagnosed in about 75 to 150 children each year in the United States. More than 50% of all ependymomas are diagnosed during childhood. In adults, ependymomas of the spine account for over half of all spinal tumors. The occurrence of ependymomas is equal among all races.

Causes and symptoms

As is the case for most brain tumors, the cause of ependymoma is unknown. Ependymal cells usually grow in an orderly and controlled way, but if for some reason this process is disrupted, the cells continue to divide and form a tumor. Research is being carried out to identify possible contributing factors. Little is known, but researchers have begun to make progress in the areas of genetic, hereditary, and environmental causes.

The first symptoms of any type of brain tumor are usually due to increased pressure within the skull. This may be the result of a blockage in the ventricles of the brain causing a buildup of CSF or may be induced by swelling around the tumor itself. The increased pressure can cause headaches, vomiting and visual problems. Symptoms specific to ependymomas include swelling of the optic nerve, rapid and jerky eye movements, neck pain and irritability. Seizures, fits and personality changes are also general symptoms associated with a brain tumor. About 25% of children with ependymomas have seizures. Other ependymoma symptoms depend on which area of the brain is affected.

- If located in the frontal lobe of the brain, ependymomas may cause mood swings, personality changes, and paralysis on one side of the body.
- If occurring on the temporal lobe of the brain, coordination, speech, and memory problems may result.
- If located on the parietal lobe of the brain, the condition may affect writing and related tasks.
- If located in the cerebellum, ependymomas may cause unsteady gait and problems with coordination and balance.

Diagnosis

To plan treatment, doctors need to find out as much as they can about the type, location, and size of the ependymoma. A number of diagnostic tests and examinations are scheduled. The first test is a neurological examination to evaluate any effect the tumor may have had on the nervous system. Every patient with ependymoma is usually subjected to diagnostic imaging of the spinal cord and brain. The most sensitive method available for evaluating spinal cord **metastasis** is spinal **magnetic resonance imaging** (MRI) performed with gadolinium, a contrast agent injected into the patient before the procedure. Other imaging studies—such as a CT scan—may also be performed to find the exact location and size of the ependymoma. To confirm the diagnosis, a **biopsy** will be perfomed and an ependymoma specimen will be examined under a microscope. Ependymomas sometimes spread from their original location through the CSF. An additional test called a myelogram may be done to check for this condition and to see if the tumor has spread to the spinal cord.

Treatment team

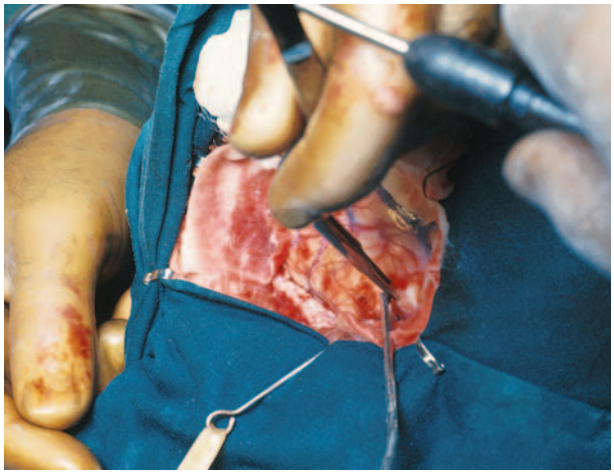
The primary physician will recommend one or more types of treatment based on the ependymoma diagnosis (size, location, type) and on the patient's medical history, age, and overall health. As a rule, the treatment team includes a neurosurgeon, a neurologist, a radiation oncologist and a medical oncologist.

Clinical staging, treatments, and prognosis

There is no formal staging system for ependymomas. They are divided into supratentorial and infratentorial tumors and treated accordingly. Treatment will proceed depending on a number of factors such as the patient's general health and age, the size and location of the ependymoma, and whether it has spread. Before any treatment is given for ependymoma, it will be important to reduce the pressure in the skull if this has occurred. If it is due to a buildup of CSF, a shunt may be inserted to drain off the excess fluid. Steroid drugs may also be prescribed to reduce swelling around the ependymoma.

When possible, surgery is the first form of treatment for ependymoma. The purpose of surgery is to remove as much of the tumor as possible without damaging the healthy brain tissue. However, it may not be possible to remove it entirely and follow-up treatment may be required. One approach is to prescribe repeated surgery in patients who still have ependymoma remaining after a first surgery and **radiation therapy**.

Radiation therapy, or the use of high-energy rays to destroy the cancer cells, is often used after surgery to destroy any remaining cancer cells. It may also be used alone to treat ependymomas that cannot be reached by surgery. Since ependymomas may spread to the spinal cord, radiation therapy is sometimes given to both the brain and spinal cord. Radiation oncologists are also using focal radiation techniques, meaning that they give a single large dose of radiation so as to kill residual cancer cells after regular radiation therapy in patients who have significant tumor tissue remaining after surgery.



A brain surgery in progress. When possible, surgery is the first form of treatment for ependymoma. *(Custom Medical Stock Photo. Reproduced by permission.)*

Chemotherapy, or the use of anti-cancer drugs to destroy cancer cells, is another form of treatment indicated for ependymomas. It may be given alone or in conjunction with surgery and radiation therapy. Newer and improved chemotherapeutic drugs are now being used after surgery, with the goal of shrinking the ependymoma before radiation therapy.

Postoperative radiation therapy has definitely been shown to improve chances of recovery, but results of chemotherapy are considered somewhat disappointing. Age is also a factor in recovery. Usually, the younger the patient, the less favorable the prognosis. The best recoveries usually occur in patients who have no visible tumor after surgery.

Alternative and complementary therapies

In a search for less toxic therapies and improved quality of life, patients with primary brain tumors are increasingly considering complementary and alternative treatments. The American Brain Tumor Association provides a list of therapies such as acupuncture, antioxidant therapy, acupressure, meditation, etc. However, the association does not officially endorse any of them. The

treatment team will be able to offer the best advice as to whether alternative and/or complementary treatments are indicated.

Coping with cancer treatment

Learning to live with ependymoma can be difficult for both patient and family. Several national associations exist to educate, support and advocate for families of children with cancer, survivors of childhood cancer, and the health professionals who care for them. These organizations offer contacts with peer-support groups and distribute a wealth of cancer-related brochures and publications.

Clinical trials

In 2001, the National Cancer Institute supported over 33 ependymoma **clinical trials** to evaluate a variety of new treatments. The National Cancer Institute monitors clinical trials and should be contacted for up-to-date information.

Prevention

A large, coordinated investigation recently carried out in Europe, Israel, and North America studied the factors that might affect the occurrence of primary brain tumors in infants and children under the age of 20. Conclusions were that women taking vitamin supplements containing C, A, E, and/or folate during the entire period of their pregnancy were half as likely to have their child develop a brain tumor before age 5, as compared to those who did not take **vitamins**.

Special concerns

Recurrence of an ependymoma is very dependent upon the extent of surgical removal as well as on the success of the treatment course following the initial diagnosis. Most recurrent ependymomas occur in the vicinity of the cavity from which the original tumor was surgically removed. Treatment options for an individual with a recurrent ependymoma usually include more surgery, chemotherapy, and further radiotherapy. An ependymoma can also metastasize into adjacent areas of the brain or, less commonly, to distant parts of the central nervous system. Approximately 12% of patients will have evidence of metastasis at the time of diagnosis. In these situations, more extensive treatment is used to treat the disease.

Children diagnosed with ependymomas are the object of special concern because of their vulnerability to radiation therapy. The organs in children are, generally speaking, significantly more sensitive to radiation than those of adults. Thus, radiation doses delivered to a child may have devastating side effects and must therefore be designed so as to address the issues of toxicity as well as that of treatment efficiency.

KEY TERMS

Brain—One of the two parts of the central nervous system (CNS). It is responsible for the control of body activities and the interpretation of information obtained from the senses. The brain is the center of thoughts and emotions.

Brain ventricles—Four connected hollow cavities in the brain.

Central nervous system (CNS)—In humans, the CNS consists of the brain, cranial nerves, and spinal cord.

Cerebrospinal fluid (CSF)—A clear, colorless fluid that fills the ventricles of the brain and contains small quantities of glucose and proteins. It bathes the brain and spinal cord.

Cerebellum—Part of the brain responsible for somatic motor function, the control of muscle tone and maintenance of balance.

Cerebrum—Part of the brain where thought and higher functions reside.

Ependymal cells—These cells line the ventricles within the central part of the brain, and thus form part of the pathway through which cerebrospinal fluid travels.

Frontal lobe—Part of the brain responsible for higher thought processes.

Metatastis—The transfer of cancer from one location or organ to another one not directly related to it.

Metatastic brain cancer—Tumors that start in other organs and then spread to the brain.

Primary brain cancer—Cancers that start in the brain.

Parietal lobe—One of two brain hemispheres responsible for associative processes.

Spinal cord—Elongated part of the central nervous system of vertebrates that lies in the vertebral canal and from which the spinal nerves emerge.

Temporal lobe—Part of the brain located below the cerebrum and responsible for auditory (hearing) and receptive processes.

QUESTIONS TO ASK THE DOCTOR

- Where is the ependymoma located?
- What is the next step? Are more tests necessary
- What kinds of specialists should I seek out for treatment?
- What medication is necessary, and what is it for? What are the side-effects?
- Considering age and the extent of the ependymoma, what is the current prognosis?

When the ependymoma causes blockage of CSF flow and leads to hydrocephalus, a special tubing called a ventriculo-peritoneal shunt (VP shunt) can be surgically implanted in the brain ventricles to drain the excess CSF into the abdomen. This procedure allows the fluid to bypass the tumor blockage and relieves the pain and symptoms of hydrocephalus.

See also Imaging studies; Brain and Central nervous system tumors; Childhood cancers.

Resources

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PERIODICALS

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Smyth, M., B. Horn, C. Russo, and M. Berger. "Intracranial Ependymomas of Childhood: Current Management Strategies."*Pediatric Neurosurgery* 33 (September 2000): 138-50.

ORGANIZATIONS

American Brain Tumor Association. 2720 River Rd., Des Plaines, IL 60018. (800) 886-2282. <http://www.abta.org>.

American Cancer Society. 1599 Clifton Road N.E., Atlanta, GA 30329. (800) 227-2345. <http://www.cancer.org>.

Brain Surgery Information Center. <http://www.brain-surgery.com>.

Cancer Research Institute. 681 Fifth Avenue, New York, NY 10022. (800)992-2623. <http://www.cancerresearch.org>.

Candlelighters Childhood Cancer Foundation. (800) 366-2223. <http://www.candlelighters.org>.

National Cancer Institute's Cancer Information Service. (800) 4-CANCER.

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Dictionary for Brain Tumor Patients. ABTA Publication. [cited June 21, 2001]. <http://www131.rapidsite.net/abtaor/information/dictionary.htm>.

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Monique Laberge, Ph.D.

Epirubicin

Definition

Epirubicin is a semi-synthetic anthracycline-based anticancer (or antineoplastic) drug derived from **doxorubicin**. It is also known by its trade name Ellence.

Purpose

Epirubicin is used as the **chemotherapy** agent for adjuvant therapy in patients diagnosed with **breast cancer**, and, as determined by the attending oncologist, epirubicin may be used in the treatment of lung, gastric, and pancreatic cancers.

Description

Epirubicin has been used extensively since the mid-1980s for both early stage and metastatic breast cancer. Epirubicin received Federal Drug Administration approval in the fall of 1999 for adjuvant therapy in patients with node-positive breast cancer. Like other DNA- interactive antineoplastic family members, epirubicin binds to DNA to inhibit DNA, RNA, and protein synthesis resulting in cell death. It has been demonstrated that epirubicin also acts to block cell growth and to increase the production of cytotoxic free radicals. For breast cancer treatment, epirubicin has proven highly effective when administered as a single agent in a sequential regimen. Epirubicin may be given in combination with **cyclophosphamide**, and 5-fluorouracil; however, currently there is no clinical evidence to suggest that long-term survival is greater in the combination regimen than with epirubicin alone. The lower

toxicity associated with epirubicin treatment promotes better quality of life for the patient.

Recent research has examined the role of epirubicin in treating prostate cancer. Study of its effects in helping to relieve pain, quality of life, and survival are preliminary, but it appears that eprirubicin is not effective alone in treating metastatic prostate cancer. A study in 2003 reported that epirubicin, used in combination with cancer drugs cisplatin and irinotecan, might have promising broad antitumor activity. In the future, epirubicin might be used in combination therapies to treat many types of tumors.

Recommended dosage

Epirubicin is administered as a red fluid via intravenous injection (IV) into a cannula placed into the vein or through a central line inserted under the skin into a vein near the collarbone. The dose of epirubicin prescribed will vary among patients, correlated with patient body size, the purpose of the dose, whether the epirubicin will be used as a single agent or in combination, and the stage and aggressiveness of the cancer type. A starting dose of 50 mg/m^2 of body surface per dose cycle of epirubicin is an appropriate regimen. Treatment cycles may be given weekly. With higher doses, cycles may be reduced to only two to three times per month. The maximum cumulative dose for anthracyclines is defined by cardiotoxicity. Studies on epirubicin have only been conducted on adult patients; therefore, with the associated risk of cardiotoxicity there are no recommendations for dosage on young children or the elderly.

Precautions

To maximize treatment effects, patients receiving epirubicin should observe certain guidelines. Along with any specific modifications given by the oncologist, these guidelines should include monitoring the area surrounding the injection site, and regular laboratory testing for white blood cell count, and kidney, liver, and bone marrow function. In order to reduce the possibility of immunosupression, immunizations not approved or prescribed by the oncologist should be avoided. Those receiving epirubicin should avoid contact with individuals taking, or that have recently taken, oral polio vaccine or individuals that have an active infection. When necessary, a protective facemask can be worn. Specific instructions on oral hygiene procedures to reduce the risk of gum abrasion should be received. Avoiding touching the eye and nasal areas unless hands have been properly washed immediately prior to contact is advised. To reduce bleeding and bruising complications, patients should exercise extreme caution when handling sharp instruments and decline participation in contact sports. The oncologist may suggest increased fluid intake to prevent kidney problems and to ensure proper kidney function.

Prior to treatment, the patient's medical history should be thoroughly reviewed to avoid complications that might arise from previous conditions such as bone marrow depression; viral, fungal, or bacterial infection; heart, kidney disease, or liver disease; or tumor cell infiltration of bone marrow. The oncologist should also be made aware if the patient is pregnant, if there is the possibility the patient might be pregnant, or if the patient is a breast-feeding mother. Only prescribed medications or over the counter (OTC) drugs approved by the oncologist should be taken by a patient receiving epirubicin

Side effects

Along with the desired anticancer effects from epirubicin treatment, less desirable side effects are to be anticipated. All presenting side effects should be discussed with the oncologist. Some side effects may occur that do not require medical attention, but nonetheless concern the patient. These commonly include hair loss (alopecia), lack of menstrual periods, discolored urine, **nausea and vomiting**, occasional **diarrhea**, hot flashes,

KEY TERMS

Adjuvant therapy—Treatment that is prescribed to increase the effectiveness of a primary treatment.

Anthracycline—Drugs that have a characteristic four-ring structure that are linked, via a glycosidic bond, to daunosamine, an amino sugar, which are used in leukemia therapy to prevent cell division by disrupting the structure of the DNA.

Antineoplastic—Agents that inhibit or prevent the maturation and proliferation of malignant cells.

Cytotoxic—A term that refers to chemicals that are directly toxic to a cell, preventing the growth or reproduction of the cell.

Doxorubicin—An extremely effective anticancer drug isolated from the *Streptomyces peucetius* bacteria.

Free radicals—Highly reactive molecules that act as agents of tissue damage.

Oncologist—A physician who specializes in the diagnosis and treatment of cancer patients.

and temporary decrease of bone marrow function. Less frequently, the patient also may experience loss of appetite with accompanying **weight loss**, darkening of the soles of the feet, palms, or nails, and cardiotoxicity. Most of these side effects disappear with the end of treatment or may be eased during treatment with prescribed intervention from the oncologist.

Other side effects from epirubicin treatment require immediate attention from a healthcare professional. These indicators of potentially life-threatening conditions or medical overdose frequently include bleeding and bruising; the presence of ulcers, sores, or redness in the mouth, throat, or on the lips; a cough or hoarseness; pain or difficulty in urination; **fever** or chills; lower back or side pain; black tarry stools; redness or drainage from the eyes or eye area; pinpoint red spots on the skin; and red streaks around the injected vein. More rare, but no less critical side effects may include wheezing or shortness of breath; joint pain; fast or irregular heartbeat; skin rash or **itching**; discoloration, redness, or warmth at the site of the injection; swelling in feet, legs, and abdomen; and tenderness of the abdomen or lymph nodes.

Interactions

More than 70 regularly prescribed drugs are known to have interactive effects with epirubicin. A complete and exhaustive list should be documented in the patient's history prior to treatment. In particular, the patient should be made aware of specific drugs that, when given concurrently with epirubicin, produce increased problems and risks in the following areas:

- liver problems
- blood disorders
- risk of infection
- risk of heart damage and heart failure
- extended clearance time of epirubicin from the body
- risk of secondary leukemia

Resources

PERIODICALS

"Cisplatin, Irinotecan, and Epirubicin Have Promising Broad Antitumor Activity." *Cancer Weekly* October 14, 2003: 12.

"Epirubicin Alone Should Not be Used to Treat Hormone-Resistant Prostate Cancer." *Drug Week* October 31, 2003: 333.

Jane Taylor-Jones, Research Associate, M.S.

epoietin alfa *see* **Erythropoietin**

Epstein-Barr virus

Definition

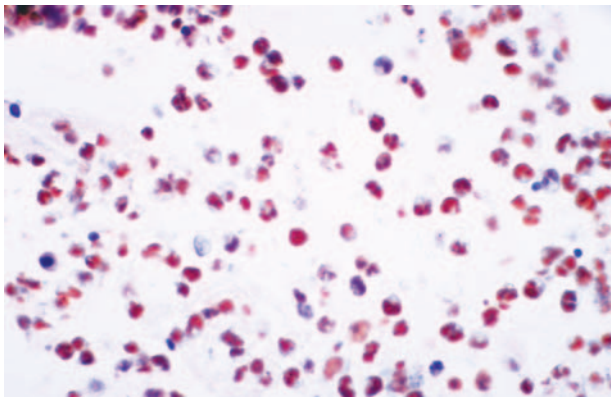
Epstein-Barr Virus, or EBV, is the name given to a member of the herpesvirus family that is associated with a variety of illnesses—from infectious mononucleosis (IM), to nasal-pharyngeal cancer, and **Burkitt's lymphoma**.

Description

Herpesviruses have long been known. The name actually comes from the Greek adjective *herpestes*, which means creeping. Many herpesvirus species appear to establish a life-long presence in the human body, remaining dormant for long periods and becoming active for some, often inexplicable, reason. EBV is only one of several members of the Herpesvirus family that have similar traits. Others include varicella zoster virus—the cause of both chickenpox and shingles—, and the **herpes simplex** virus responsible for both cold sores and genital herpes. EBV is usually transmitted through saliva but not blood, and is not normally an airborne infection.

EBV occurs in nearly all regions of the world, and is considered among the most common infectious viruses known to humankind. In the United States, the Center for Disease Control (CDC) estimates that 95% of adult Americans between the ages of 35 and 40 years have been infected, but it is less prevalent in children and teenagers. This pattern of infecting adults more than children persists throughout other prosperous western countries, but does not hold true in underdeveloped regions such as Africa and Asia. In Africa, most children have been infected by EBV by the age of three years

Individuals with EBV infections typically show some elevation in the white blood cell count and a noticeable increase in lymphocytes—white blood cells associated with the **immune response** of the body. IM is a time-limited infection that usually lasts from one to two months. Symptoms include **fever**, malaise, sore throat, swollen glands and (sometimes) swollen spleen and/or liver. EBV infections that lead to Burkitt's lymphoma in Africa typically affect the jaw and mouth area, while the (very rare) incidences of Burkitt's lymphoma found in developed countries are more apt to manifest tumors in the abdominal region. **Nasopharyngeal cancer** is uncommon in the West but more prevalent in the Far East. It affects more men than women, and usually occurs between the ages of 40 and 50 years.



Epstein-Barr virus in situ. *(Custom Medical Stock Photo. Reproduced by permission.)*

Causes

EBV has been linked to IM in the Western world for decades. It has also become associated consistently with nasopharyngeal cancers in Asia (especially China) and Burkitt's lymphoma in Africa and Papua New Guinea. According to the CDC, EBV is not the sole cause of these two malignancies, but does play an important role in the development of both cancers. The mechanism that allows Epstein-Barr Virus to at least help in producing such diverse illnesses in diverse regions of the world has been the subject of increasing research and scrutiny.

It is known that, once it infects a person, EBV is one of the herpesviruses that remain in the human body for life. Under certain, still not-understood conditions, it alters white blood cells normally associated with the immune system, changing B lymphocytes (those normally associated with making antibodies), and causing them to reproduce rampantly. EBV can bind to these white blood cells to produce a solid mass made up of B lymphocytes—called Burkitt's lymphoma—or to the mucous membranes of the mouth and nose and cause nasopharyngeal cancer. Since Burkitt's lymphoma typically occurs in people living in moist, tropical climates, the same regions where people usually contract malaria, it has been speculated that the immune system is altered by its response to malaria. When EBV infection occurs, the altered immune system's reaction is the production of a tumor.

Special concerns

Though studies about the hereditary tendency of abnormal cell development after EBV infection are incomplete, some studies have shown it to be a hereditary trait based upon the X chromosome.

KEY TERMS

Lymphocyte—Any of a group of white blood cells of crucial importance to the immune system's production of a tailor-made defense against specific invading organisms.

Lymphoma—A group of cancers in which the cells of tissue usually found in the lymph nodes or spleen multiply abnormally.

Malaria—A serious disease prevalent in the tropics. It is caused by parasites and produces severe fever and sometimes complications affecting the kidneys, liver, brain, and blood. It is spread by the Anopheles mosquito and can be fatal.

Nasopharyngeal—Affecting the passage connecting the nasal cavity behind the nose to the top of the throat behind the soft palate.

Treatments

Because EBV infections are viral in origin, **antibiotics** are ineffective against them. Much research is geared toward the development of a **vaccines** effective against both the virus and cancer.

Anticancer drugs, such as **cyclophosphamide**, or **radiation therapy** have been shown to be effective against Burkitt's lymphoma in four out of five cases.

Alternative and complementary therapies

The goal of alternative treatment is to lower the white blood cell count to normal levels. Treatment often includes nutritional supplements such as flaxseed oil or shark cartilage, vitamins—including **vitamins** C and K, and mineral supplements containing magnesium and potassium. Well-conducted randomized **clinical trials** have not yet been conducted to prove efficacy of these therapies.

Resources

ORGANIZATIONS

Center for Disease Control, National Center for Infectious Diseases *Epstein-Barr Virus and Infectious Mononucleosis*. [cited March 26, 2001]. <http://www.cdc.gov.org>.

Queensland Institute of Medical Research. [cited December 7, 1999]. <http:www.webmaster@qimr.edu.au>.

Joan Schonbeck, R.N.

QUESTIONS TO ASK THE DOCTOR

- What tests can be done if Epstein-Barr Virus infection is suspected?
- Have any vaccines against Epstein-Barr Virus been developed?

ERCP *see* **Endoscopic retrograde cholangiopancreatography**

ERCP stenting *see* **Stenting**

Erlotinib

Definition

Erlotinib is a biological therapy used to interrupt cell division and slow the growth of tumors.

Purpose

Erlotinib is used to treat advanced **non-small cell lung cancer** (NSCLC), an aggressive type of lung cancer. NSCLC the most common type of lung cancer. It is most often caused by exposure to tobacco smoke. The World Health Organization (WHO) estimates that NSCLC is responsible for about 880,000 deaths each year. Lung cancer is the leading cause of cancer deaths in the United States. The American Cancer Society estimates that lung cancer is responsible for 28% of cancer deaths or the deaths of more than 160,000 individuals annually. Erlotinib is not a first-line treatment for NSCLC, and is used only after the cancer has failed to respond or stopped responding to at least one round of **chemotherapy**.

Description

Erlotinib is a man-made treatment that combines natural human and animal substances to target specific cells in the body. It sold in the United States under the brand name Tarceva or OSI 744 and is produced jointly by OSI Pharmaceuticals and Genentech. Erlotinib was approved for use by the United States Food and Drug Administration (FDA) in November 2004. Generic substitutes are not available.

Erlotinib works by interrupting the complex chemical pathway that stimulates cells to grow and multiply. Cancer cells grow and divide with abnormal rapidity. One strategy to slow cancer is to interrupt the information pathway that causes this wild growth. Erlotinib works in this way.

The body produces substances called growth factors that tell cells when it is time to divide and spread. Many cells, including cancer cells, have receptors on their surfaces for a growth factor called epidermal growth factor (EGF). Normally when EGF locks on to an epidermal growth factor receptor on the surface of a cell, it stimulates the production of the enzyme tyrosine kinase. Tyrosine kinase is a key chemical in telling the cell to begin growing and dividing. In the healthy body, EGF plays a role in wound healing and tissue maintenance and repair. Cancer cells are especially sensitive to EGF and appear to over-respond and grow excessively when stimulated by this growth factor.

Erlotinib does not block the production of EGF. Instead, it binds to the EGF receptors on the surface of both normal and malignant cells. Because EGF can no longer attach to the receptors, the cells are not stimulated to produce tyrosine kinase and cell growth is slowed or stopped. Erlotinib does not cure cancer, but it has been shown to prolong survival times.

As of 2005, erlotinib was being tested in more than three dozen **clinical trials** in combination with other drugs to treat many other types of metastic cancer including brain tumors, head and neck tumors, **esophageal cancer**, inoperable kidney and corectal, and solid tumors in children and adults. Information on current clinical trials that are enrolling patients can be found at <http://www.clinicaltrials.gov>.

Recommended dosage

Erlotinib comes in 25 mg, 100 mg, and 150 mg tablets that are taken once daily for as long as the cancer responds to treatment. Tablets must be taken with a large glass of water at least one hour before or two hours after a meal. The standard dose is 150 mg, although this dose may be adjusted based on the individual's health, other drugs being administered, and the development of side effects.

Precautions

Erlotinib may cause birth defects in a developing fetus. It should not be used by women who are pregnant, breastfeeding, or trying to become pregnant. Both men and women who are sexually active should use contraception while taking erlotinib.

KEY TERMS

Cornea—The clear membrane covering the eye.

Interstitial lung disease (ILD)—A serious inflammation of the lining of the air spaces (alveoli) of the lungs that causes lung scaring and shortness of breath.

Erlotinib is broken down and deactivated in the liver. Individuals with liver disease should discuss the use of erlotinib with their physician.

Side effects

The most serious side effect reported from use of erlotinib is the development of potentially fatal interstitial lung disease (ILD). Other rare but serious side effects include inflammation or abscess of the cornea of the eye and bleeding from the digestive system.

More common but less serious side effects include, but are not limited to:

- rash on the face and upper body
- loss of appetitive, nausea, vomiting, and diarrhea
- fatigue
- headache
- sore mouth
- cough and shortness of breath
- abnormal liver function tests

Interactions

Although formal drug interaction studies have not been completed, a number of drugs are suspected of interacting with erlotinib. Too much erlotinib may cause a toxic reaction. Individuals taking certain drugs may need to take a reduced dose of erlotinib. The following drugs may increase the amount of erlotinib circulating in the body:

- atazanavir (Reyataz)
- clarithromycin (Biaxin)
- indinavir (Crixivan)
- itraconazole (Sporanox)
- ketoconazole (Nizoral)
- mefazodone (Serzone)
- nelfinavir (Viracept)
- ritoavir (Norvir)
- saquinavir (Invirase; Fortovase)
- telithromycin (Ketek)
- voriconazole (VFEND)

Too little erlotinib in the body may result in failure to slow cell growth. The following drugs may decrease the effects of erlotinib. Individuals taking these drugs may need to take an increased dose of erlotinib.

- carbamazepin (Tegretol)
- phenobarbitol
- phenytoin (Dilantin)
- rifampicin (Rifadin)
- rifabutin (Mycobutin)
- rifapentine (Priftin)
- St John's Wort (herbal remedy)

In addition, grapefruit juice may interact with erlotinib and should be avoided while taking erlotinib.

Tish Davidson, A. M.

Erythropoietin

Definition

Erythropoietin, which is also referred to by the names Epogen, Procrit, epoetin alfa, and EPO, is a medicine used to treat a low red blood cell count.

Purpose

Erythropoietin is a drug approved by the Food and Drug Administration (FDA) to treat low red blood cell counts called **anemia**. This anemia can be caused by cancer **chemotherapy** treatment, kidney failure, or a drug used to treat AIDs. Erythropoietin has also been used to increase the red blood cell count in patients who are anemic and scheduled to have surgery. This can decrease the risk of needing blood transfusions.

Description

Erythropoietin is a natural substance made by the kidneys in the body. Sometimes the body cannot make enough erythropoietin to cause red blood cells to be produced. The synthetic drug erythropoietin can be given to act like the natural erythropoietin and increase red blood cells.

Chemotherapy drugs destroy cancer cells, but they also destroy normal cells in the bone marrow. Oxygen, which is needed by the body to make energy, is carried

to cells by the red blood cells. The destruction of the red blood cells causes anemia, which can make patients feel tired or dizzy.

Erythropoietin acts to stimulate the bone marrow to make more red blood cells. Patients need an adequate supply of iron in the body for erythropoietin to work best. If a patient's iron is low, the doctor may recommend oral iron tablets to keep the level of iron up. The increase in red blood cell levels should be seen in two to six weeks after beginning therapy in cancer-related anemia patients. When the red blood cell count rises, patients generally feel better.

Recommended dosage

Erythropoietin is a clear, colorless liquid that must be kept refrigerated. It is administered as an intravenous injection or an injection directly underneath the skin, referred to as a subcutaneous injection. There are several dosing schedules used to treat patients with anemia.

To treat cancer-related anemia

Erythropoietin is dosed in units per kilogram of body weight, starting at 150 units per kilograms of body weight administered three times per week. This dosage can be increased to 300 units per kilogram of body weight three times per week.

Manufacturers continue to improve the effectiveness of the drug and physicians select dosage amount and frequency based on the drug type, brand, method of administration, and the individual patient's situation. Erythropoietin may be administered at a physician office or at home subcutaneously. Typically, it has been administered once a week, though in 2004, a study revealed that a form of the drug could safely be dosed every two weeks for some cancer patients, making it more convenient.

To treat patients with renal failure

Erythropoietin starting dose is 50-100 units per kilogram of body weight three times a week. This would be adjusted based on blood work and patient response.

To treat AIDS patients on the drug zidovudine

Erythropoietin starting dose is 100 units per kilogram of body weight three times per week for 8 weeks. This would be adjusted based on blood counts and patient response.

To treat patients prior to surgery

Erythropoietin starting dose is 300 units per kilogram of body weight per day for 10 days prior to surgery, the day of surgery, and four days after surgery.

KEY TERMS

Anemia—A red blood cell count that is lower than normal.

Blood transfusion—The transfer of stored blood into a patient through a vein.

Chemotherapy—Specific drugs used to treat cancer.

Food and Drug Administration—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives approval to pharmaceutical companies for commercial marketing of their products

Intravenous—To enter the body through a vein.

Subcutaneous—Underneath the initial layer of skin.

Synthetic—Artificially made; not natural.

An alternate schedule is erythropoietin 600 units per kilogram of body weight administered once weekly beginning three weeks before surgery, then a fourth dose on the day of surgery.

Surgery patients need to take iron replacement with the start of erythropoietin injections.

Precautions

Blood counts will be monitored before receiving erythropoietin and regularly while on the drug erythropoietin. This allows the doctor to determine if patients are candidates for this treatment and if the dose the patient is receiving needs to be increased or decreased.

Blood pressure should also be monitored regularly while on erythropoietin. Patients who have high blood pressure that is not under control should not use erythropoietin.

Patients may be instructed to take oral iron tablets while on erythropoietin to increase the drug's effectiveness.

It is not recommended to give erythropoietin to patients who have cancer, such as leukemias, arising from their bone marrow.

Patients with a known previous allergic reaction to erythropoietin or the drug albumin should tell their doctor.

Patients who may be pregnant or trying to become pregnant should tell their doctor before receiving erythropoietin.

Side effects

A common side effect due to erythropoietin administration is pain or burning at the site of the injection. This can be decreased by making sure that the erythropoietin is at room temperature before giving the infection. Ice can be placed in the area of injection to numb it before receiving the shot, and the site of injection should be changed with each shot.

Common side effects of patients who receive erythropoietin include **diarrhea** and swelling.

Less common side effects in cancer patients include **fever**, nausea and vomiting, **fatigue**, shortness of breath, and weakness.

Seizures have been reported in patients with kidney failure who are taking erythropoietin.

Erythropoietin can cause an increase in blood pressure, but this is uncommon in cancer patients. Blood pressure should be monitored while on this medicine.

Interactions

In clinical studies erythropoietin did not have any drug interactions.

In addition to taking oral iron replacement, patients should increase their intake of iron in their diet. This would include eating foods such as red meats, green vegetables, and eggs.

Patients should tell their doctors if they have a known allergic reaction to erythropoietin or any other medications or substances, such as foods and preservatives. Before taking any new medications, including nonprescription medications, **vitamins**, and herbal medications, the patients should notify their doctors.

Resources

PERIODICALS

"Studies: Aranesp Dosed Semiweekly Is Comparable to Epoetin Alfa Once a Week." *Obesity, Fitness & Wellness Week* July 10, 2004: 59.

Nancy J. Beaulieu, RPh., BCOP
Teresa G. Odle

Esophageal cancer

Definition

Esophageal cancer is a malignancy that develops in tissues of the hollow, muscular canal (esophagus) along which food and liquid travel from the throat to the stomach.

Description

Esophageal cancer usually originates in the inner layers of the lining of the esophagus and grows outward. In time, the tumor can obstruct the passage of food and liquid, making swallowing painful and difficult. Since most patients are not diagnosed until the late stages of the disease, esophageal cancer is associated with poor quality of life and low survival rates.

Squamous cell **carcinoma** is the most common type of esophageal cancer, accounting for 95% of all esophageal cancers worldwide. The esophagus is normally lined with thin, flat squamous cells that resemble tiny roof shingles. Squamous cell carcinoma can develop at any point along the esophagus but is most common in the middle portion.

Adenocarcinoma has been increasing, and, among white males in the U.S., incidence of adenocarcinoma is almost equal to that of squamous cell carcinoma. Adenocarcinoma originates in glandular tissue not normally present in the lining of the esophagus. Before adenocarcinoma can develop, glandular cells must replace a section of squamous cells. This occurs in **Barrett's esophagus**, a precancerous condition in which chronic acid reflux from the stomach stimulates a transformation in cell type in the lower portion of the esophagus.

A very small fraction of esophageal cancers are melanomas, **sarcomas**, or lymphomas.

Demographics

There is great variability in the incidence of esophageal cancer with regard to geography, ethnicity, and gender. The overall incidence is increasing. About 13,000 new cases of esophageal cancer are diagnosed in the United States each year. During the same 12-month period, 12,000 people die of this disease. It strikes between five and ten North Americans per 100,000. In some areas of China the cancer is endemic.

Squamous cell carcinoma usually occurs in the sixth or seventh decade of life, with a greater incidence in African-Americans than in others. Adenocarcinoma develops earlier and is much more common in white patients. In general, esophageal cancer occurs more frequently in men than in women.

Causes and symptoms

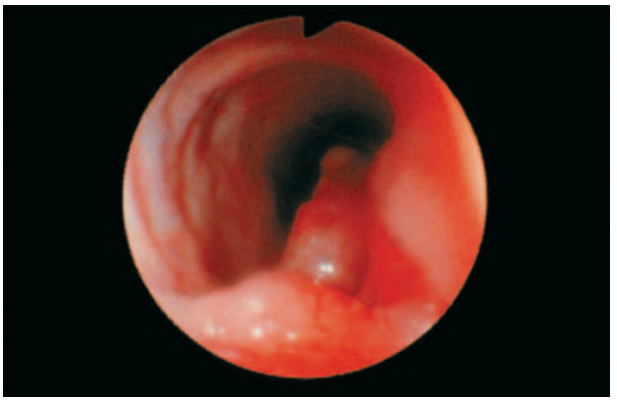
Causes

The exact cause of esophageal cancer is unknown, although many investigators believe that chronic irrita-

tion of the esophagus is a major culprit. Most of the identified risk factors represent a form of chronic irritation. However, the wide variance in the distribution of esophageal cancer among different demographic groups raises the possibility that genetic factors also play a role.

Several risk factors are associated with esophageal cancer.

- Tobacco and **alcohol consumption** are the major risk factors, especially for squamous cell carcinoma. Smoking and alcohol abuse each increase the risk of squamous cell carcinoma by five-fold. The effects of the two are synergistic, in that the combination of smoking and alchohol increases the risk by 25- to 100- fold. It is estimated that drinking about 13 ounces of alcohol every day for an extended period of time raises the risk of developing esophageal cancer by 18%. That likelihood increases to 44% in individuals who also smoke one or two packs of **cigarettes** a day. Smokeless tobacco also increases the risk for esophageal cancer.
- Gastroesophageal reflux is a condition in which acid from the stomach refluxes backwards into the lower portion of the esophagus, sometimes causing symptoms of heartburn. In some cases of gastroesophageal reflux, the chronic exposure to acid causes the inner lining of the lower esophagus to change from squamous cells to glandular cells. This is called Barrett's esophagus. Patients with Barrett's esophagus are roughly 30 to 40 times more likely than the general population to develop adenocarcinoma of the esophagus.
- A diet low in fruits, vegetables, zinc, riboflavin, and other **vitamins** can increase risk of developing to esophageal cancer.
- Caustic injury to the esophagus inflicted by swallowing lye or other substances that damage esophageal cells can lead to the development of squamous cell esophageal cancer in later life.
- Achalasia is a condition in which the lower esophageal sphincter (muscle) cannot relax enough to let food pass into the stomach. Squamous cell esophageal cancer develops in about 6% of patients with achalasia.
- Tylosis is a rare inherited disease characterized by excess skin on the palms and soles. Affected patients have a much higher probability of developing esophageal cancer than the general population. They should have regular screenings to detect the disease in its early, most curable stages.
- Esophageal webs, which are protrusions of tissue into the esophagus, and diverticula, which are outpouchings of the wall of the esophagus, are associated with a higher incidence of esophageal cancer.



A close-up view of a cancerous esophageal tumor. *(Copyright S. Benjamin. Custom Medical Stock Photo. Reproduced by permission.)*

Symptoms

Unfortunately, symptoms generally don't appear until the tumor has grown so large that the patient cannot be cured. Dysphagia (trouble swallowing or a sensation of having food stuck in the throat or chest) is the most common symptom. Swallowing problems may occur occasionally at first, and patients often react by eating more slowly and chewing their food more carefully and, as the tumor grows, switching to soft foods or a liquid diet. Without treatment, the tumor will eventually prevent even liquid from passing into the stomach. A sensation of burning or slight mid-chest pressure is a rare, often-disregarded symptom of esophageal cancer. Painful swallowing is usually a symptom of a large tumor obstructing the opening of the esophagus. It can lead to regurgitation of food, **weight loss**, physical wasting, and malnutrition. Anyone who has trouble swallowing, loses a significant amount of weight without dieting, or cannot eat solid food because it is too painful to swallow should see a doctor.

Diagnosis

A barium swallow is usually the first test performed on a patient whose symptoms suggest esophageal cancer. After the patient swallows a small amount of barium, a series of x rays can highlight any bumps or flat raised areas on the normally smooth surface of the esophageal wall. It can also detect large, irregular areas that narrow the esophagus in patients with advanced cancer, but it cannot provide information about disease that has spread beyond the esophagus. A double contrast study is a barium swallow with air blown into the esophagus to improve the way the barium coats the esophageal lining. Endoscopy is a diagnostic procedure in which a thin lighted tube (endoscope) is passed through the mouth, down the throat, and into the esophagus. Cells that appear abnormal are removed for **biopsy**. Once a

diagnosis of esophageal cancer has been confirmed through biopsy, staging tests are performed to determine whether the disease has spread (metastasized) to tissues or organs near the original tumor or in other parts of the body. These tests may include **computed tomography**, endoscopic ultrasound, **thoracoscopy**, **laparoscopy**, and **positron emission tomography**.

Treatment team

The treatment team includes the surgeon, radiologist, radiation therapist, and oncologist. Nutrition therapists are also vital in optimizing a diet that the patient can swallow easily.

Clinical staging, treatments, and prognosis

Staging

Stage 0 is the earliest stage of the disease. Cancer cells are confined to the innermost lining of the esophagus. Stage I esophageal cancer has spread slightly deeper, but still has not extended to nearby tissues, lymph nodes, or other organs. In Stage IIA, cancer has invaded the thick, muscular layer of the esophagus that propels food into the stomach and may involve connective tissue covering the outside of the esophagus. In Stage IIB, cancer has spread to lymph nodes near the esophagus and may have invaded deeper layers of esophageal tissue. Stage III esophageal cancer has spread to tissues or lymph nodes near the esophagus or to the trachea (windpipe) or other organs near the esophagus. Stage IV cancer has spread to distant organs like the liver, bones, and brain. Recurrent esophageal cancer is disease that develops in the esophagus or another part of the body after initial treatment.

Treatment

Treatment for esophageal cancer is determined by the stage of the disease and the patient's general health. The most important distinction to make is whether the cancer is curable. If the cancer is in the early stages, cure may be possible. If the cancer is advanced or if the patient will not tolerate major surgery, treatment is usually directed at palliation (relief of symptoms only) instead of cure.

SURGERY The most common operations for the treatment of esophageal cancer are esophagectomy and esophagogastrectomy. Esophagectomy is the removal of the cancerous part of the esophagus and nearby lymph nodes. This procedure is performed only on patients with very early cancer that has not spread to the stomach. Esophagogastrectomy is the removal of the cancerous part of the esophagus, nearby lymph nodes, and the upper part of the stomach. The resected esophagus is replaced with the stomach or parts of intestine so the patient can swallow. These procedures can significantly relieve symptoms and improve the nutritional status of more than 80% of patients with dysphagia. Although surgery can cure some patients whose disease has not spread beyond the esophagus, but more than 75% of esophageal cancers have spread to other organs before being diagnosed. Less extensive surgical procedures can be used for palliation.

CHEMOTHERAPY Oral or intravenous **chemotherapy** alone will not cure esophageal cancer, but pre-operative treatments can shrink tumors and increase the probability that cancer can be surgically eradicated. Palliative chemotherapy can relieve symptoms of advanced cancer but will not alter the outcome of the disease.

RADIATION External beam or internal radiation, delivered by machine or implanted near cancer cells inside the body, is only rarely used as the primary form of treatment. Post-operative radiation is sometimes used to kill cancer cells that couldn't be surgically removed. Palliative radiation is effective in relieving dysphagia in patients who cannot be cured. However, radiation is most useful when combined with chemotherapy as either the definitive treatment or preoperative treatment.

KEY TERMS

Computed tomography—A radiology test by which images of cross-sectional planes of the body are obtained.

Endoscopic ultrasound—A radiology test utilizing high frequency sound waves, conducted via an endoscope.

Laparoscopy—Examination of the contents of the abdomen through a thin, lighted tube passed through a small incision.

Positron emission tomography—A radiology test by which images of cross-sectional planes of the body are obtained, utilizing the properties of the positron. The positron is a subatomic particle of equal mass to the electron, but of opposite charge.

Synergistic—The combined action of two or more processes is greater than the sum of each acting separately.

Thoracoscopy—Examination of the contents of the chest through a thin, lighted tube passed through a small incision.

Palliation

In addition to surgery, chemotherapy, and radiation, other palliative measures can provide symptomatic relief. Dilatation of the narrowed portion of the esophagus with soft tubes can provide short-term relief of dysphagia. Placement of a flexible, self-expanding stent within the narrowed portion is also useful in allowing more food intake.

Follow-up treatments

Regular barium swallows and other **imaging studies** are necessary to detect recurrence or spread of disease or new tumor development.

Prognosis

Since most patients are diagnosed when the cancer has spread to lymph nodes or other structures, the prognosis for esophageal cancer is poor. Generally, no more than half of all patients are candidates for curative treatment. Even if cure is attempted, the cancer can recur.

Alternative and complementary therapies

Photodynamic therapy (PDT) involves intravenously injecting a drug that is absorbed by cancer cells and kills them after they are exposed to specific laser beams. PDT can be used for palliation, but it also cured some early esophageal cancers during preliminary studies. Researchers are comparing its benefits with those of more established therapies.

Endoscopic laser therapy involves delivering short, powerful laser treatments to the tumor through an endoscope. It can improve dysphagia, but multiple treatments are required, and the benefit is seldom long-lasting.

Coping with cancer treatment

Many cancer patients have found it helpful to discuss cancer and treatment with other cancer patients and survivors in support groups. Guidance from a nutritionist may be helpful to maintain a balanced diet and to ensure that the patient is receiving adequate **nutritional support**. The hospital staff and treatment team may be valuable resources for locating support groups and other community resources.

Clinical trials

Researchers are searching more effective chemotherapeutic agents and radiation treatment regimens. Many studies are aimed at defining the most beneficial combination of surgery, chemotherapy, and radiation in the treatment of esophageal cancer.

Prevention

There is no known way to prevent esophageal cancer.

Resources

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National Coalition for Cancer Survivorship. 1010 Wayne Avenue, 5th Floor, Suite 300, Silver Spring, MD 20910. Telephone: 1-888-650-9127.

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Essiac

Definition

Essiac is a medically untested and unproven alternative treatment for cancer, AIDS, and other diseases. It consists of a blend of four herbs: burdock root (arctium lappa), Indian rhubarb root (rheum palmatum, sometimes known as Turkish rhubarb), sheep sorrel (rumex acetosella), and the inner bark of slippery elm (ulmus fulva or ulmus rubra).

Purpose

Essiac tea is generally used by alternative healthcare practitioners to treat various forms of cancer and the side effects of conventional cancer therapy. It is also used to treat AIDS. It is used to a lesser extent to treat a variety of other medical conditions, including diabetes, skin inflammation, liver and thyroid problems, **diarrhea**, ulcers, and some other degenerative diseases. Other uses include treating pain, purifying the blood, healing wounds, lowering cholesterol, and increasing energy levels. As of 2005, essiac tea is more commonly used in Canada than the United States.

Although each of the four main ingredients in essiac tea are used to treat other conditions, only the sorrel is used separately to treat cancer. Only when the four are combined do they effect anticancer properties. Alternative healthcare practitioners do not claim to know how or why the ingredients work in combination, but one idea is that they work synergistically to stimulate production of antibodies. Rene Caisse (pronounced "Reen Case", d. 1978), a Canadian nurse who ran her own clinic from 1934 to 1942, was convinced that this tea could cure cancer. She believed essiac tea purified the blood and carried away damaged tissue and infection related to the cancer. She also believed the tea strengthened the immune system, allowing healthy cells to destroy cancerous cells.

Caisse maintained that tumors not destroyed by essiac tea would be shrunk and could be surgically removed after six to eight weeks of treatment. To insure any malignant cells that remained after treatment and surgery were destroyed, Caisse recommended at least three months of additional weekly essiac treatments.

One of Caisse's patients was her mother, Friseide Caisse, who was diagnosed with **liver cancer** at the age of 72. Her mother's physician reportedly said she had only days to live. Rene Caisse began giving her mother daily intramuscular injections of the tea. Friseide began recovering within a few days and after a few months, with less frequent doses of essiac, her cancer was gone. She lived to be 90, finally succumbing to heart disease.

Description

Essiac tea is based on a Canadian Ojibwa Indian formula containing primarily burdock root, Turkish rhubarb root, sheep sorrel, and the inner bark of the slippery elm. It is used in alternative medicine mainly as a treatment for cancer.

The formula, said to have been first developed by an Ojibwa healer, was intended to purify the body and balance the spirit. In 1922, the formula came to the attention of Rene Caisse (essiac is Caisse spelled backwards), a nurse in Ontario, Canada, after hearing first-hand accounts of its curative effects on cancer. She began administering the tea to cancer patients and found it to have remarkable healing abilities. Despite considerable objection from the medical profession, Caisse continued treating cancer patients with the tea until she died in 1978. In 1977, Caisse sold the essiac tea formula to the Resperin Corp. of Ontario, Canada. It is now produced generically by at least 35 companies and sold mainly in health food stores and on the Internet. It is sold as a dry mix and as a brewed liquid.

Caisse reported that hundreds of her patients had been cured of their cancers through the use of her tea, sometimes used as intramuscular injections. Most of the patients came to her after conventional cancer treatments (surgery, **chemotherapy**, and **radiation therapy**) failed. Several alternative healthcare practitioners report essiac tea seems to work best in patients who have had the least amount of radiation therapy or chemotherapy.

The mainstream medical community does not embrace essiac tea. Critics contend that a certain number of cancers deemed incurable spontaneously go into remission without adequate medical explanation. Others chalk up the successes to the so-called placebo effect, in which the belief that the treatment is working effects a cure rather than the treatment itself. The treatment is not approved by the American Medical Association or the American Cancer Society. In 2000, the U.S. Federal Trade Commission (FTC) began a crackdown on Internet distributors of essiac tea. The FTC said claims by the distributors that essiac tea cured or was an effective treatment for cancer, AIDS, and other diseases were misleading and illegal.

In 1938, a bill in the Canadian Parliament to legalize essiac tea failed by three votes. As of 2005 the tea still is not approved for marketing in the United States or Canada. However, the Canadian Health and Welfare Department permits compassionate use of essiac tea on an emergency basis.

In 1975 and again in 1982, the Memorial Sloan-Kettering Cancer Center in New York tested only the sorrel component in the tea. They boiled it, which may have neutralized any beneficial compounds in the leftover tea, and administered it to mice with cancerous tumors. It determined the formula had no anticancer effects. The National Cancer Institute and Canadian Bureau of Prescription Drugs reached the same conclusion in the 1980s.

Recommended dosage

The four main ingredients of essiac tea are sold separately and can be combined at home. Essiac tea is also marketed as tea bags and in bottles of the prepared formula. The formula is ready to use immediately. When ready, the bottle is shaken to mix the sediments. Four tsp of the essiac formula are blended with 4 tsp of warm spring water. The usual daily dosage is 2–4 oz of tea for persons weighing 100–150 pounds and 2 oz for every 50 pounds over 150 pounds. Some alternative health practitioners recommend regular doses of essiac to strengthen the immune system and as a preventative for certain diseases, including cancer. The frequency ranges from daily to weekly.

Precautions

Essiac tea is not recommended for pregnant or lactating women. The formula should not be prepared or stored in plastic or aluminum containers. Sunlight and freezing temperatures are believed to destroy the formula's effectiveness. It is generally recommended that persons consult with their physician before treating any condition with essiac. It is important to remember that essiac is often used in combination with traditional cancer treatments, such as chemotherapy, radiation, and surgery.

Side effects

No major adverse side effect have been associated with essiac tea.

Interactions

Essiac is not known to adversely interact with other medications or nutritional supplements.

Estramustine

Definition

Estramustine is a combination of two drugs, estradiol and **mechlorethamine**, that is used to slow the growth of and kill malignant cells in **prostate cancer**. It is also known by the brand names Emcyt and Estracyte.

Purpose

Estramustine is used in the palliative treatment of metastatic or progressive cancer of the prostate. Palliative treatment helps to relieve symptoms, but does not cure the cancer.

In the early 2000s, estramustine is also being investigated in several clinical trials evaluating its usefulness in managing asymptomatic prostate cancer patients; its effectiveness in combination with docetaxel as an alternative to radical prostatectomy; and its usefulness in increasing the effectiveness of a microtubule drug in treating prostate cancer. These studies suggest that estramustine may have beneficial applications outside the field of palliative care.

Description

Estramustine is classified as an antineoplastic drug. Estramustine is a combination of two drugs: estradiol, a potent female hormone (estrogen), and mechlorethamine, a nitrogen mustard. Its action is to decrease **testosterone**, increase estrogen level, and suppress cell growth. Estramustine is approved by the United States Food and Drug Administration (FDA) for the palliative treatment of metastatic or progressive cancer of the prostate.

KEY TERMS

Chemotherapy—The use of chemical agents to treat or control diseases, especially cancer.

Cholesterol—A steroid alcohol found in human cells and body fluids, implicated in the onset of heart disease.

Degenerative diseases—Diseases characterized by progressive degenerative changes in tissue, including arteriosclerosis, diabetes mellitus, and osteoarthritis.

Diabetes—A degenerative disease characterized by inadequate production or absorption of insulin, excessive urine production, and excessive amounts of sugar in the blood and urine.

Recommended dosage

As with many cancer-fighting drugs, the dose of estramustine a patient receives is individualized and depends on the patient's body weight and general health, as well as what other **chemotherapy** drugs are being used. A standard dose of estramustine is 14 mg per kg of body weight per day, divided into three or four doses. This is equivalent to one 140 mg capsule for each 22 lbs (10 kg) of body weight. It takes one to three months for estramustine to start to work. The therapy is continued as long as the patient has a favorable response. Some patients have successfully taken this drug for as long as three years.

Precautions

Estramustine should not be used by men who have a history of problems with blood clots, a blood clotting disorder, or allergic reactions to estrogen or nitrogen mustard.

Estramustine must be taken more than one hour before or more than two hours after meals. It should not be taken with dairy products, calcium supplements, of any food that is high in calcium.

Patients taking estramustine should avoid having any vaccinations while taking the drug, and should consult their doctor immediately if exposed to chicken pox

KEY TERMS

Malignant—Cancerous. Cells tend to reproduce without normal controls on growth and form tumors or invade other tissues.

Metastatic—Spreading of cells from the original site of the cancer to other parts of the body where secondary tumors are formed.

Palliative—Serving to relieve or alleviate the symptoms of a disease or disorder without curing the disease.

or measles, as this drug may make them more susceptible to these diseases.

Side effects

Nausea and vomiting can occur within 2 hours of taking estramustine. This side effect is mild and patients will respond to **antiemetics** to control the nausea and vomiting. **Diarrhea** and flatulence can occur while taking this drug. Patients taking estramustine also have an increased risk of developing blood clots, congestive heart failure, and heart attacks, although these side effects are rare. Therefore, men with a history of blood clots and heart disease require frequent monitoring while receiving this drug. Estramustine also decreases the glucose (sugar) tolerance in people with diabetes, and frequent blood sugar monitoring is recommended in this patient population. Blood pressure may also be increased with estramustine, and monitoring of blood pressure is recommended, especially in patients with a history of high blood pressure. Men receiving estramustine may also experience enlargement of their breasts due to the estrogen component in the drug combination. Patients may also experience decreased sexual drive, although this side effect is reversible. If sexually active, the patient should use a contraceptive method (even if he is impotent) prior to initiating therapy, because estramustine may reverse impotency while on the drug. Estramustine may also cause genetic mutations. Therefore, use of contraceptive measures is advisable. Other side effects include lethargy, rash, **itching**, dry skin, easy bruising, flushing, and thinning hair. If any of the above side effects occur, patients should alert their physician to these side effects immdediately.

Serious side effects that require immediate medical attention include:

- sudden or severe headaches
- sudden shortness of breath or difficulty breathing
- increased weight gain or swelling of the feet or legs
- pain in the chest
- sudden pain or cramping in the legs or calves
- weakness or numbness in the legs or arms

Interactions

Dairy products and other foods containing calcium interfere with the absorption of estramustine. Prior to treatment, patients should notify their physician about any medications they are taking and of any known allergies.

Patients taking estramustine should not use tobacco products, as smoking causes the blood vessels to narrow and may increase the risk of circulation problems during treatment with estramustine..

Estramustine intensifies the effects of vinblastine, another anticancer drug.

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Etidronate *see* **Bisphosphonates**

Etoposide

Definition

Etoposide is a **chemotherapy** medicine used to treat cancer by destroying cancerous cells. Etoposide is also sold under the brand name VePesid.

Purpose

Etoposide is approved by the Food and Drug Administration (FDA) to treat refractory **testicular cancer** and small cell lung cancer. It has also been useful for other types of cancer, including non-small cell cancer, leukemia (acute myeloocytic leukemia), Hodgkin's and non-Hodgkin's **lymphoma**, muscle, brain tumors, bladder, stomach, **Kaposi's sarcoma**, **Ewing's sarcoma**, **Wilms' tumor**, **multiple myeloma**, hepatoma, uterine carcinoma, myeloblastoma, **mycosis fungoides**, **neuroblastoma**, and **prostate cancer**. It is presently being studied as a treatment for lung cancer that hsa metastasized to the central nervous system.

Description

Etoposide is formulated as a clear liquid for infusion into a vein and it is also available as a pink capsule form to be taken by mouth. It may also be referred to as VP-16, VP-16-213, and epipodophyllotoxin. Etopophos is a different formulation of the intravenous form of etoposide. Etoposide was originally derived from a plant and has been made for longer than 20 years. Etoposide is a member of the group of chemotherapy drugs known as topoisomerase II inhibitors. Topoisomerase II inhibitors cause breaks in the genetic material (DNA) inside the cancer cells and prevent them from further dividing and multiplying. Then the cells die.

The oral form of etoposide is preferred for longer cycles of treatment, while the intravenous form is used primarily for short-term infusion. Studies indicate that lower doses of oral etoposide are utilized by the body more efficiently than higher doses.

Recommended dosage

An etoposide dose can be determined using a mathematical calculation that measures a person's body surface area (BSA). This number is dependent upon a patient's height and weight. The larger the person, the greater the body surface area. BSA is measured in the units known as square meter (m^2). The body surface area is calculated and then multiplied by the drug dosage in milligrams per square meter (mg/m^2). This formula is used to calculate the actual dose a patient is to receive.

To treat refractory testicular cancer

Etoposide injection dosed at the range of 50–100 mg per square meter per day given into a vein over 30–60 minutes daily for 5 consecutive days, every 3–4 weeks. This is done in combination with other chemotherapy drugs, **cisplatin** and **bleomycin**.

Etoposide can also be dosed at 100 mg per square meter per day injected into a vein over 30–60 minutes on day 1, day 3, and day 5.

To treat lung cancer

Etoposide injection dosed at the range of 35 mg per square meter per day is given into a vein infused over 30–60 minutes for 4 consecutive days. It is dosed up to 50 mg per square meter per day given into a vein infused over 30–60 minutes for 5 days in a row. This is usually in combination with other chemotherapy drugs such as cisplatin or **carboplatin**.

Etoposide phosphate formulation is dosed the same as etoposide, but administered over a shorter period of time. The formulation is often used in transplant patients because it does not need to be mixed in large amounts of intravenous fluid and can be administered over less than 30 minutes, unlike regular etoposide.

Oral etoposide 50mg capsules for lung cancer are dosed by doubling the intravenous dose and rounding the number to the nearest 50 mg.

Patients with kidney problems may receive smaller doses of etoposide than patients with normal kidneys. The doctor will monitor a patient's kidney function prior to therapy by checking certain blood counts. Patients with liver abnormalities may also need dose adjustments of the etoposide.

Precautions

Blood counts will be monitored regularly while on etoposide therapy. During a certain time period after receiving etoposide, there is an increased risk of getting infections. Caution should be taken to avoid unnecessary exposure to crowds and people with infections.

Patients with a known previous allergic reaction to chemotherapy drugs should tell their doctor.

Patients who may be pregnant or are trying to become pregnant should tell their doctor before receiving etoposide. Chemotherapy can cause men and women to be sterile, or unable to have children.

Patients should check with their doctors before receiving live virus **vaccines** while on chemotherapy.

KEY TERMS

Anemia—A red blood cell count that is lower than normal.

Chemotherapy—Specific drugs used to treat cancer.

Deoxynucleic acid (DNA)—Genetic material inside of cells that carries the information to make proteins that are necessary to run the cells and keep the body functioning smoothly.

Food and Drug Administration (FDA)—The government agency that oversees public safety in relation to drugs and medical devices, and gives the approval to pharmaceutical companies for commercial marketing of their products.

Intravenous—To enter the body through a vein.

Neutropenia—A white blood cell count that is lower than normal.

Refractory cancer—Cancer that is not responding to treatment.

Patients who develop mouth sores from etoposide treatment should discontinue smoking, drinking alcohol, and eating highly acidic or spicy foods.

Side effects

The most common side effect from etoposide is low blood counts (**myelosuppression**). When the white blood cell count is low (**neutropenia**), patients are at an increased risk for developing a **fever** and infections. Etoposide also causes the platelet count to fall. Platelets are blood cells in the body that allow for the formation of clots. When the platelet count is low, patients are at an increased risk for bruising and bleeding. Low red blood cell counts (**anemia**), may also occur due to etoposide administration. Low red counts may make patients feel tired, dizzy, and lacking in energy.

Etoposide infusions, if given too quickly into the vein, can cause a significant drop in blood pressure. This can usually be avoided by administering the etoposide over a time period of at least 30–60 minutes. A patient's blood pressure may be taken when receiving an etoposide infusion. To minimize dizziness from a drop in blood pressure, the patient should sit up slowly following an etoposide infusion.

Etoposide can cause mild to moderate **nausea and vomiting**. This is more common in patients taking the oral capsules. Patients will be given **antiemetics** before receiving etoposide to help prevent or decrease this side effect. Hair loss (**alopecia**) is common with etoposide administration. **Diarrhea**, loss of appetite (anorexia), and mouth sores are less common but have been reported to occur.

Liver problems may occur due to etoposide administration, though they are mild. The liver returns to normal when the drug is stopped. This side effect is more common with higher etoposide doses.

Males receiving etoposide for testicular cancer typically have a lowered sperm count during chemotherapy. As with liver function, however, testicular function gradually returns to normal after etoposide treatment is stopped. In one group of 38 patients treated for testicular cancer, 13 fathered a total of 16 children within two years after the end of etoposide treatment. None of the children had any birth defects.

Less common neurological side effects caused by etoposide include tingling and numbness of the fingers and toes, dizziness, headache, sleepiness, visual disturbances, and confusion.

Other less common side effects caused by etoposide include rash, **itching**, sores in the mouth, darkening skin, fever, development of another type of cancer or leukemia, redness and pain at the site of injection into the vein, chest pain, and irregular heart rate.

Rare side effects from using etoposide are allergic, or anaphylactic-type, reactions, which include fever, chills, tongue swelling, shortness of breath, low blood pressure, and increased heart rate.

Interactions

Etoposide, if given with the oral drug **warfarin** (also known as coumadin), can increase bleeding.

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American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657-3000. <www.ashp.org>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

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Ewing's sarcoma

Definition

Ewing's sarcoma is a cancer that affects children, teens, and less often, young adults. It begins in developing bone cells. Ewing's sarcoma cells grow uncontrollably and form masses or lumps called tumors. They can start in any bone in the body but about half of all cases involve flat bones such as the pelvic bones and the long bones in the leg—the tibia, fibula, and femur.

Description

Ewing's sarcoma is the second most common bone tumor among children and teens. It accounts for about 1% of all **childhood cancers**. This cancer is named for James Ewing, the researcher who first described the tumor in 1921. There are some rare cases of Ewing's sarcoma that do not begin in bones. These tumors are thought to start in nerve or other soft tissues.

Demographics

Ewing's sarcoma occurs most frequently in children ages 11 to 15 years old. Slightly more males than females develop Ewing's sarcomas, and like **osteosarcoma**, the most common bone cancer found in children, it is more often diagnosed in taller teens. The disease is rarely diagnosed in children younger than 5 or adults older than 30. It affects primarily Caucasians, and rarely occurs in African Americans and native Chinese.

Causes and symptoms

The causes of Ewing's sarcoma are not known. It is possible that certain inherited conditions increase the risk of developing this cancer.

About two–thirds of patients with Ewing's sarcoma have a painful swelling or lump that can be felt in the affected bone. Along with tenderness, the area of swelling may be hot. The symptoms depend on the site of the tumor and whether it has spread. For example, a tumor on a rib may cause painful breathing. When Ewing's sarcoma has spread, patients may have other symptoms such as **fatigue**, **weight loss**, and **fever**.

Diagnosis

Most patients who have Ewing's sarcomas go to the doctor because they have discovered a lump or mass or swelling on or near a bone. Others have symptoms related to the part of the body that is affected by the tumor, such as pressure on the bladder from a tumor on a pelvic bone.

The patient's doctor will take a detailed medical history to find out about the symptoms. The history is followed by a complete physical examination with special attention to the suspicious symptom or body part.

Depending on the location of the tumor (mass or lump), the doctor will order **imaging studies** such as **x ray**, **computed tomography** (CT) scans and **magnetic resonance imaging** (MRI) to help determine the size, shape and exact location of the tumor. The doctor will also order a chest x ray to find out if the tumor has spread to the lungs, and bone scans to determine if the tumor has spread to bones. Blood tests will be done and an examination of the bone marrow will be performed to see if the marrow is involved.

A **biopsy** of the tumor is necessary to make a diagnosis of Ewing's sarcoma. During a biopsy, some tissue from the tumor is removed. The tissue sample is examined by a pathologist, a doctor who specializes in the study of diseased tissue.

Types of biopsy

The type of biopsy done depends on the location of the tumor. For some small tumors, such as those on the arm or leg, the doctor may perform an excisional biopsy,

A femur of a patient diagnosed with Ewing's sarcoma. Ewing's sarcoma is the second most common bone tumor among children and teens, and half of all cases involve flat or long bones, such as the femur. *(Custom Medical Stock Photo. Reproduced by permission.)*

removing the entire tumor and a margin of surrounding normal tissue. Most often, the doctor will perform an incisional biopsy, a procedure that involves cutting out only a piece of the tumor. This biopsy provides a core of tissue from the tumor that is used to confirm the diagnosis of Ewing's sarcoma.

Treatment team

Like other cancer patients, teens and young adults with Ewing's sarcoma are usually cared for by a multidisciplinary team of health professionals. The patient's pediatrician, family physician, or primary care doctor may refer the patient to other physician specialists, such as surgeons and oncologists (doctors who specialize in cancer medicine). Radiologic technicians perform x ray, CT and MRI scans and nurses and laboratory technicians may obtain samples of blood, urine and other laboratory tests.

Before and after any surgical procedures, including biopsies, specially trained nurses will explain the procedures and help to prepare patients and families. Depending on the tumor location and treatment plan, patients may also benefit from rehabilitation therapy with physical therapists and nutritional counseling from dieticians.

Clinical staging, treatments, and prognosis

Staging

The purpose of staging a tumor is to determine how far it has advanced. This is important because treatment varies depending on the stage. Generally, stage is determined by the size of the tumor, whether the tumor has spread to nearby lymph nodes, whether the tumor has spread elsewhere in the body, and what the cells look like under the microscope.

There is no commonly accepted system for staging Ewing's sarcomas. As is the case with other cancers, patients with metastases (spread) tend to have worse outlooks than patients whose tumors have not spread.

Between one quarter to one third of patients with Ewing's sarcoma have metastases when they are first diagnosed. Patients with tumors closer to the trunk of the body or in the pelvic bones are more likely to have metastases than patients with tumors located on the lower leg or foot. The most common sites for spread of Ewing's sarcoma are to the lungs or bones.

Treatment

Treatment for Ewing's sarcoma varies depending on the location of the tumor, its size and grade, and the extent of its spread. For most patients, the goals of treatment are to remove or control the tumor and combat the spread of the cancer.

'Generally, when removing the tumor will not sharply reduce function, Ewing's sarcoma tumors are surgically removed. The goal of removing as much tumor as possible is to reduce the amount of radiation needed after surgery. The part of the body where the tumor was removed is treated with radiation to destroy remaining tumor cells. Most patients also receive **chemotherapy**, powerful anti–cancer drugs to destroy remaining cancer cells.

When the disease has spread throughout the body, there may be no benefit from surgical removal of the tumor. These patients, who have widespread metastases, are treated with radiation and chemotherapy.

SIDE EFFECTS The surgical treatment of Ewing's sarcoma carries risks related to the surgical site, such as loss of function resulting from loss of a long bone in the leg. There also are the medical risks associated with any surgical procedure, such as reactions to general anesthesia or infection after surgery.

The side effects of **radiation therapy** depend on the site being radiated. Radiation therapy can produce side effects such as fatigue, skin rashes, nausea and **diarrhea**. Most of the side effects lessen or disappear completely after the radiation therapy has been completed.

The side effects of chemotherapy vary depending on the medication, or combination of anticancer drugs, used. Chemotherapy drugs often given to combat Ewing's sarcoma are **cyclophosphamide**, **doxorubicin**, **vincristine**, and **dactinomycin**.

For patients with widespread disease, chemotherapy may be given along with bone marrow transplant and radiation to the entire body. Nausea and vomiting, **anemia**, lower resistance to infection, and hair loss (alopecia) are common side effects of chemotherapy. Medication may be given to reduce the unpleasant side effects of chemotherapy.

Alternative and complementary therapies

Many patients find that alternative and complementary therapies help to reduce the stress associated with illness, improve immune function and feel better. While there is no evidence that these therapies specifically combat disease, activities such as biofeedback, relaxation, therapeutic touch, massage therapy and guided imagery have been reported to enhance well–being.

Prognosis

The outlook for patients with Ewing's sarcoma varies, depending on the size and volume of the tumor, its stage, and the extent of its spread. Patients with large tumors do not fare as well as those with smaller tumors. Patients with tumors in certain sites, such as the bones of the pelvis and spinal column also seem to have poor outlooks because by the time these tumors are discovered they have already spread.

Ewing's sarcoma may spread locally to areas near the tumor and it can spread to nearby lymph glands. To spread to distant parts of the body, the cancer cells travel in the blood, bone marrow or through the lymph glands. In general, tumors that have spread widely throughout the body are not associated with favorable survival rates.

Nearly three quarters of patients diagnosed before the cancer has spread are disease free for five years after treatment. Patients with tumors that do not respond to treatment and those who suffer recurrences have poor outlooks for long–term survival.

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of cancerous cells or by killing them.

Metastasize—The spread of cancer cells from a primary site to distant parts of the body.

Oncologist—A doctor who specializes in cancer medicine.

Pathologist—A doctor who specializes in the diagnosis of disease by studying cells and tissues under a microscope.

Radiation therapy—Treatment using high energy radiation from x–ray machines, cobalt, radium, or other sources.

Stage—A term used to describe the size and extent of spread of cancer.

Coping with cancer treatment

Teens undergoing cancer treatment have special needs. The diagnosis of a life–threatening illness, surgery and radiation or chemotherapy may cause fear, anxiety, **depression** and loss of self–esteem. Disruption of normal routines and discomfort from diagnostic tests and treatment may also cause anxiety. There are additional social problems including making up missed school work, explaining the illness and treatment to friends, and coping with physical limitations or disability.

Teens with serious illnesses and disabilities face emotional conflicts and psychological challenges. One conflict is between the teen's growing desire for independence and the reality of dependence on others for the activities of daily living. It is important for teens to be fully informed about their disease and treatment plan and involved in treatment decision making. Many teens benefit from continuing contact with friends, classmates, teachers, and family during hospital stays and recovery at home.

Depression, emotional distress, and anxiety associated with the disease and its treatment may respond to counseling from a mental health professional. Individual

QUESTIONS TO ASK THE DOCTOR

- How big is the tumor?
- Has the Ewing's sarcoma spread?
- What are the recommended treatments?
- What are the side effects of the recommended treatments?
- Is treatment expected to cure the disease or only to prolong life?

and group therapy often help teens and young adults to reveal and express their feelings about illness and treatment. Many cancer patients and their families find participation in mutual aid and group support programs help to relieve feelings of isolation and loneliness. By sharing problems with others who have lived through similar difficulties patients and families can exchange ideas and coping strategies.

Clinical trials

More than 25 clinical studies were underway during 2001. For example, at John Hopkins Oncology Center and other cancer centers across the United States, patients with recurring or widespread Ewing's sarcoma were being given chemotherapy to stop tumor cells from dividing as well as stem cells (bone marrow transplantation) to replace immune cells killed by chemotherapy.

Other **clinical trials** compare different combinations of drugs used for chemotherapy or combinations of chemotherapy and radiation to find out which combination is more effective. For example, in one study, patients with Ewing's sarcoma were randomly assigned to two different treatment groups. One group received chemotherapy followed by surgery and radiation therapy. The other group received radiation therapy during chemotherapy.

Other types of clinical research study individuals and families at high risk of cancer to help identify cancer genes. To learn more about clinical trials visit the National Cancer Institute (NCI) web site at http://cancertrials.nci.nih.gov or the Pediatric Oncology Branch of the National Cancer Institute web site at http://www.dcs.nci.nih.gov/pedonc/

Prevention

Since the causes of Ewing's sarcoma are not known, there are no recommendations about how to prevent its development. Among families with an inherited tendency to develop soft tissue sarcomas, careful monitoring may help to ensure early diagnosis and treatment of the disease.

Special concerns

Ewing's sarcoma, like other cancer diagnoses, may produce a range of emotional reactions in patients and families. Education, counseling and participation in group support programs can help to reduce feelings of guilt, fear, anxiety and hopelessness. For many parents suffering from spiritual distress, visits with clergy members and participation in organized prayer may offer comfort.

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American Cancer Society. 1599 Clifton Road, N.E., Atlanta, GA 30329. (800)227–2345.

Cancer Research Institute. 681 Fifth Avenue, New York, NY 10022. (800)992–2623.

National Cancer Institute Clinical Cancer Trials. <http://cancertrials.nci.nih.gov>.

National Cancer Institute (National Institutes of Health). 9000 Rockville Pike, Bethesda, MD 20892. (800)422–6237.

The Pediatric Oncology Branch of the National Cancer Institute. (877) 624–4878 or (301)496–4256. <http://www.dcs.nci.nih.gov/pedonc/>.

Barbara Wexler, M.P.H.

Exemestane *see* **Aromatase inhibitors**

Exenteration

Definition

An exenteration is a major operation during which all the contents of a body cavity are removed. Pelvic exenteration refers to the removal of all the organs and adjacent structures of the pelvis, and orbital exenteration

refers to the removal of the entire contents of the ocular orbit, sometimes including the eyelids as well.

Purpose

The pelvis is the basin-shaped cavity that contains the bladder, rectum and reproductive organs. (The reproductive organs include the ovaries, uterus and cervix for women and the prostate for men.) Pelvic exenteration is performed to surgically remove cancer that involves these organs and that has not responded well to other types of treatment. For example, pelvic exenteration might be performed for primary **rectal cancer** because 5%–10% of primary rectal cancers spread to nearby pelvic organs. Pelvic exenteration is also indicated when cancer returns after an earlier treatment, as rectal cancer does in some 20% of cases. In women, the operation is additionally performed mostly for advanced and invasive cases of endometrial, ovarian, vulvar, vaginal and **cervical cancer**, and in men for aggressive **prostate cancer**.

Similarly, orbital exenteration is performed to remove the eye and surrounding tissues when cancer of the orbital contents cannot be controlled by simple removal or irradiation. It is often the only course of treatment for advanced **basal cell carcinoma** of the eyelids, for cancers that have spread to the optic nerve, or retinoblastomas larger than 1/4 inch (0.6 cm), as well as for large tumors of the eyeball.

Exenteration is not only a major operation for a patient to undergo, it is also technically very challenging, because it involves elaborate **reconstructive surgery**. It is a radical surgical procedure, but it often provides the only opportunity available for patients to eliminate the cancer and to prevent cancer from recurring.

Precautions

Pelvic exenterations should not be performed on patients diagnosed with inflammation of the roots of spinal nerves, sciatica, lymphedema, liver cancer, extrapelvic disease, and obstructions of the urinary tract.

All precautions applying to major surgery apply to exenterations, whether pelvic or ocular.

After pelvic exenteration, sexual intercourse should be avoided as directed by the surgeon. This is to allow the wound to heal properly.

Description

Pelvic exenteration

There are three types of pelvic exenterations.

KEY TERMS

Anus—The terminal orifice of the gastrointestinal (GI) or digestive tract which includes all organs responsible for getting food in and out of the body.

Catheter—Long thin tubes that carry urine from the kidneys to the bladder.

Conjunctiva—A clear membrane that covers the inside of the eyelids and the outer surface of the eye.

Cyst—Any closed cavity surrounded by a wall made up of cells joined by cementing substances and that contains liquid or semi-solid material.

General anesthesia—Method used to stop pain from being felt during an operation. General anesthesia is the most powerful type and is generally used only for major operations, such as brain, neck, chest, abdomen, and pelvis surgery.

Ocular orbit—Bony cavity containing the eyeball.

Resection—The complete or partial removal of an organ or tissue.

Rectum—The last part of the large intestine (colon) that connects it to the anus.

ANTERIOR EXENTERATION This operation usually removes in women the uterus, bladder, vagina, and entire urethra. Patients selected for this operation have cancers that are located so as to allow the rectum to be spared. Vaginal reconstruction is performed afterwards if required. It is called anterior because it removes organs toward the front or in front of the pelvis.

POSTERIOR EXENTERATION This operation removes in women the uterus, ovaries, Fallopian tubes, anus, supporting muscles and ligaments, and all the vagina except a portion of the wall that supports the urethra. In men, the bladder is also removed. It is called posterior because it removes organs located in the back part of the pelvis.

TOTAL PELVIC EXENTERATION This operation removes the bladder, rectum and anus, supporting muscles and ligaments, together with either the prostate in men or the gynecologic (reproductive) organs in women. Total pelvic exenteration is performed when there is no opportunity to perform a less extensive operation, because of the location and size of the cancer. For women, vaginal reconstruction is performed, which also helps reconstruction of the pelvic area. In both anterior and total pelvic exenteration, a urinary tract can be constructed.

QUESTIONS TO ASK THE DOCTOR

- Why do I need the operation?
- What are the benefits of having the operation?
- What are the risks of having the operation?
- What if I don't have this operation?
- Where can I get a second opinion?
- What has been your experience in doing the operation?
- How long will it take me to recover?
- What are the surgeon's qualifications?

The exact surgical procedure followed depends on the type of exenteration, but generally, all pelvic exenterations start with an incision in the lower abdomen. Blood vessels are clamped and the organs specified by the procedure are removed. The site of incision is then stitched up.

Orbital exenteration

This operation removes the eyeball and surrounding tissues of the orbit. The eye is surrounded by bone, so orbital exenteration is easier to tolerate than pelvic exenteration and patients may even undergo the operation as outpatients. Orbital exenteration with partial preservation of eyelids and conjunctiva can sometimes be achieved. Within two weeks of surgery, patients are usually fitted with a temporary ocular prothesis (plastic eye). Later, facial prostheses are also attached to the facial skeleton.

Both pelvic and orbital exenterations are performed using general anesthesia.

Preparation

The evaluation of patients before pelvic exenteration includes a thorough physical exam with rectal and pelvic examination. **Endorectal ultrasound** and **imaging studies**, such as **computed tomography** scans (CT scans) and **magnetic resonance imaging** (MRI), are routinely used to obtain pictures of the abdominal and pelvic areas and evaluate the spread of the cancer.

Ocular ultrasound examination, CT scan and **angiography** evaluation is usually performed to prepare for ocular exenteration.

Preparing for the operation usually depends on the type of exenteration procedure selected. Most patients receive a combination of **radiation therapy** and **chemotherapy** before the operation. Surgery is typically performed approximately six weeks later.

In the case of pelvic exenteration, patients are required to clean as much waste as possible out of the large intestine, using various **laxatives** or enemas. This cleaning of the colon and rectum is required so as to eliminate stool and lower the level of bacteria, thus preventing infections after surgery. **Antibiotics** are also typically given to help sterilize the colon.

Aftercare

Pelvic exenteration

After a pelvic exenteration, a drainage tube is inserted at the site of the incision. There usually is some bleeding, discharge and considerable tenderness and pain for a few days. This is a major operation that requires at least a three- to five-day hospital stay. Side effects depend on the type of pelvic exenteration performed, but always include urination difficulty, especially if adjustment to a catheter is required, and a very painful lower abdomen.

Some exenterations require a temporary or permanent **colostomy**, meaning the creation of an opening (stoma) in the abdomen to allow solid waste to leave the body. Permanent colostomy may be needed, for example, if the rectum is removed. In such cases, the patient needs time to adjust and be taught how to irrigate, empty, clean and wear the colostomy bags.

Stitches are usually removed from the skin on the third day or before the patient is sent home. A prescription for pain medication is usually given as well as instructions for follow up care.

Ocular exenteration

After ocular exenteration, most patients have a headache for several days which goes away using medication such as tylenol. An eye ointment is also prescribed that contains antibiotics and steroids to help the healing process.

Risks

No surgical procedure is risk-free. Complications are always possible, especially if the operation is major. As with any operation, possible exenteration risks include possible complications due to the anesthetic and wound infection.

In the case of pelvic exenteration, the following complications are also possible:

- hemorrhage that may require a blood transfusion

- injury to the bowel
- urinary tract infection
- urinary retention requiring permanent use of a catheter
- bowel obstruction
- urinary tract infection

The following considerations also apply: after removal of the reproductive organs, women will no longer have monthly periods nor will they be able to become pregnant. For men, surgery involving the prostate and the nerves around the rectum may also result in the inability to produce sperm or to have an erection.

In the case of orbital exenteration, the following complications have been known to occur:

- growth of an orbital cyst (rare)
- chronic throbbing orbital pain
- sinusitis (nasal stuffiness)
- ear problems

See also Adenocarcinoma; Cervical cancer; Endometrial cancer.

Resources

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Women's Health Matters. <http://www.womenshealthmatters.ca/centres/cancer/cervical/treatment/index.html>.

Monique Laberge, Ph.D.

Extracranial germ cell tumors

Definition

Extracranial **germ cell tumors** are reproductive cells that have developed into a rare form of malignancy within the reproductive system or within another part of the body, outside of the brain.

Description

Germ cells are cells that develop into the reproductive organs (gonads) during a child's embryonic stage; the testicles in males, the ovaries in females. Germ, meaning "seed," refers to directly to these cells' role in production of the sperm and the ovums. On rare occasions, these calls can experience an abnormal transformation and growth, and develop into a germ cell tumor.

After normal embryonic development, germ cells travel down through the midline path of the body and enter the pelvis to form the gonads. For this reason, most germ cells tumors develop in the testes or ovaries and are referred to as gonadal germ cell tumors. However, germ cells can also migrate during the embryonic development and travel to other regions of the body. Also known as **extragonadal germ cell tumors**, these tumors can develop inside the chest, coccyx, abdomen, and pelvis. Because they grow outside the cranium (another location of possible germ cell tumor growth), these types of germ cells are commonly referred to as extracranial germ cell tumors.

Malignant extracranial germ cell tumors can also spread (metastasize) to other parts of the body. The liver, lungs, and the lymph nodes can be commonly affected by **metastasis**, but in rare cases the central nervous system and skeletal structure (bones and marrow) can also be affected. Benign extracranial germ cell tumors do not metastasize, but the increased pressure caused by their growth can damage and/or hinder the function of nearby organs and structures.

Extracranial germ cell tumors are divided into certain types, depending on their characteristics. The four most common forms of extracranial germ cell tumors include:

- Mature teratoma—The most common subtype of extracranical germ cell tumor and generally benign in nature. Mature teratomas are cysts that contain germ cell layers from the ectoderm (skin and nervous tissue), mesoderm (muscle, bone, cartilage, and connective tissue), and endoderm (the lining of the digestive and respiratory systems). As such, any type of tissue can grow within these cysts, usually of a type far different from the surrounding tissue; i.e. hair and teeth growing in the testes. Some mature tertomas can even secrete enzymes and hormones, such as insulin, androgens, and growth hormones.
- Immature teratoma—Similar to mature tertomas, but the tissues are more immature. Immature teratomas

may also contain neuroepithelium tissues (associated with the development of the nevrous system). Germ cell tumors of this classification are more likely to be malignant in nature.

- Yolk Sac tumor—The most common malignant extracranial germ cell tumor in young children. Yolk sac tumors are also the most common germ cell tumor, benign or malignant, to develop in the testes of infants and young boys. Tumors are soft and brittle with a yellow and/or grayish cystic exterior. Necrosis and extensive hemorrhaging are common experienced with yolk sac tumors.
- Germinoma—Depending on the location of tumor, germinomas are known as dysgerminoas (ovaries) and seminomas (testes). They are most common malignancy to affect the central nervous system of children.

Demographics

Approximately half of all extracranial germ cell tumors are benign in nature. Of these tumors, almost 50% of them will develop in the gonads, 25% in the coccyx, and roughly 5% in miscellaneous extragonadal locations, such as chest, stomach, liver, and central nervous system.

Extracranial germ cells tumors are particularly rare amongst young children, only accounting for approximately 3% of cancer cases for children 15 years of age and younger. However, this incidence rate rises dramatically in adolescents (aged 15 to 19 years of age) accounting for approximately 14% of cancer cases. However, in both categories, the incidence rate of extracranial germ cell tumors has been rising over the last few decades.

Causes & symptoms

The underlying cause behind the development of extracranial germ cell tumors is not fully understood. However, a number of inherited defects of the central nervous system, spine, and genitourinary (genital and urinary organs) tract have been associated with an increased risk of development. Cryptorchidism, for example, has been identified as a possible risk factor for the development of testicular germ cell tumors. Patients with Klinefelter's syndrome (a chromosomal anomaly in males) and Swyer's syndrome (a developmental problem of the gonads) are also at risk of developing extragonadal germ cell tumors in the chest and central nervous system, respectively.

Symptoms

Symptoms of extracranial germ cell tumors will great depend on the type and location of the tumor, as well as the age and gender of the patient. However, general symptoms will include:

- A growth, swelling, or mass that can be felt and/or seen
- Constipation and/or urinary retention
- Incontinence
- Leg weakness
- Abnormal testicular shape or size, sometimes painful, in boys
- Abdominal pain in girls
- Abnormal shortness of breath
- Chest pain

Diagnosis

Patients presenting with the various symptoms of extracranial germ cell tumors should be given a thorough history and careful physical examination. This examination should include blood testing and complete blood count. Germ cell tumors often produce proteins in the blood that can be used as markers. In particular, elevated levels of alpha-fetoprotein and human

KEY TERMS

Cryptorchidism—A developmental defect marked by the failure of the testes to descend into the scrotum.

Chemotherapy—The treatment of cancer using specific chemical agents and/or drugs, which are selectively destructive to malignant cells and tissues.

Hematologist—A physician specializing in the treatment of blood diseases.

Germ Cell—An ovum or a sperm cell or one of their developmental precursors.

Gonads—The male and female reproductive organs, which produce sperm (testes) and ovum (ovaries).

Oncologist—A physician specializing in the study and treatment of tumors.

Teratoma—A tumor consisting of different types of tissue, as of skin, hair, and muscle, caused by the development of independent germ cells.

Yolk sac—A membranous sac attached to an embryo, which functions as the circulatory system of the human embryo before internal circulation begins.

chorionic gonadotropin may indicate the presence of extracranial germ cell tumors. If indicated, this examination should be followed by either a **computed tomography** (CT) scan or **magnetic resonance imaging** (MRI) scan. This will provide the physician with a better picture of where the tumor is located. Chest x-rays can determine if there is tumor growth in the lungs.

If this initial examination indicated the presence of a tumor, a **biopsy** must be conducted to confirm whether or not the tumor is malignant. If the cancer cells are malignant, a pathologist can determine what grade the tumor is and estimate its growth rate. There are three grades of cell malignancy: Low (almost normal appearance, slow growth, unlikely to spread), Intermediate (average appearance and growth, may spread), and High (highly abnormal in appearance, quick growth rate, and likely to spread).

Treatment team

Children and adolescents are the most common patients to be afftected by extracranial germ cell tumors. Unlike adults, they may not always understand what is happening to them and are likely to become upset and scared by both their disease and the various stages of the diagnostic and therapeutic process. As such, children with cancer should always be treated by a multidisciplinary team of cancer specialists. In addition to their family health provider, primary care should be provided by specialists trained in treating children and adolescents, including surgical subspecialists, oncologists, hematologists, and nursing specialists. In addition, social workers and therapists, as well as rehabilitation specialists, can provide the young patient with the effective supportive care they will require during and after treatment. Quality of life should be the focus of any therapeutic regimen for child patients.

Clinical staging, treatments, and prognosis

Initial diagnosis of the germ cell tumor will help determine whether or not it is malignant or benign in nature. If a malignancy is detected, further diagnostic studies will be required to determine if the tumor has spread to other areas of the body. Staging of the tumor depends on its size and whether it has metastasized. There are four stages commonly associated with all extracranial germ cell tumors:

- Stage 1—Cancer has not spread to surrounding tissues and lymph nodes. Surgical removal of tumor will eliminate all cancer cells.
- Stage 2—Cancer has metastasized to surrounding tissues and/or lymph nodes. Surgical removal of tumor cannot eliminate all cancer cells.
- Stage 3—Cancer has metastasized to surrounding tissue, to several lymph nodes, and is present in the fluid of the abdomen. Surgical removal of tumor cannot eliminate all cancer cells.
- Stage 4—The cancer has spread to other organs of the bodTumor has spread to other areas

QUESTIONS TO ASK YOUR DOCTOR

- Is the tumor benign or malignant, and where is it located? How will that affect the prognosis?
- What risks and side effects my child could face undergoing the different treatments for this type of cancer?
- Has the malignancy spread any further than the original tumor and, if so, what parts of the body are affected?
- WHat is the likelihood the tumor will return?
- Do you know of any support groups my child and I can contact?

Treatment

Treatment will depend greatly on the stage, grade, and position of the extracranial germ cell tumor. Other factors will include the child's age, general health, medical history, and their tolerance for specific procedures and medications. Generally, treatment will involve the surgical removal of the tumor and, if required, the surrounding tissue. This is followed by either **chemotherapy** (drugs used to kill the tumor cells) and/or radiotherapy (killing the cancerous cells with radiation). To what lengths these procedures will be employed will depend on the size of the tumor and to what extent it has spread throughout the body.

Effective treatment of extracranial germ cell tumors may require the use of other modalities, including **bone marrow transplantation**, hormonal replacement, **antibiotics** and supportive and follow-up care.

Prognosis

Recent advances in treatment modalities, such as the use of Cisplatin-based chemotherapy, have provided a high five-year survival rate; between 75% and 90%. However, some types of germ cells tumors may respond differently to treatment, thus increasing or worsening the patient's prognosis. For example, germ cell tumors in

the lower back have a very low survival rate (approximately 28%) even if the malignancy is localized. Extracranial germ cell tumors can also be recurrent in nature, returning after surgical removal. The tumor may occur in the original location or another area of the body. These can occur in 20% to 30% of all high risk patients. Unfortunately, the presence of recurrent extracranial germ cell tumors offers a poor prognosis. It is important to ask the physician regarding the prognosis of each type of germ cell tumor.

Coping with cancer treatment

Special considerations should be taken with coping with the treatment of extracranial germ cell tumors, as the majority of patients will be adolescents and young children. Some adolescents may find discussing these tumors to be embarrassing. Even so, if possible, older children should be involved in all the details of their treatment. The patient will rely heavily upon family and friends for support during this difficult time. Counselors, therapists, and local support groups may also be of assistance. The goal must be to prevent fear and confusion, as well as to maintain the child's quality of life as much as possible.

Clinical trials

Due to the rarity of **childhood cancers**, all child patients should be considered for entrance into **clinical trials**. New treatments are being researched constantly. Details of current and future clinical trials can be found at the National Cancer Institute's website: <http://cancer.gov/clinicaltrials>.

Prevention

As these cancerous cells begin very early during pregnancy, there are no known preventive measures against extracranial germ cell tumors.

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Jason Fryer

Extragonadal germ cell tumors

Definition

Germ cells are primitive cells within the body that normally mature into ova (egg) or sperm cells. More than 90% of all **germ cell tumors** are gonadal; that is, they develop in the ovaries or the testes (the gonads). The remaining 5–10% of germ cell tumors arise outside of the gonads: these are the extragonadal germ cell tumors. These tumors occur mostly in the chest, lower back, and head.

Description

Extragonadal germ cell tumors are related to developmental problems that occur prior to birth. In the growing embryo, germ cells migrate to the immature ovaries or testes. In some instances, these cells fail to move to the gonads and end up in the midchest area between the lungs (mediastinum), the lowest part of the back (presacral area), or near the pea-sized gland between the two hemispheres of the brain (pineal gland). When these germ cells grow in these extragonadal sites, they sometimes develop into tumors. These tumors can be benign (noncancerous) or malignant (cancerous).

Benign extragonadal germ cell tumors are called benign teratomas. Malignant extragonadal germ cell tumors are subdivided into seminoma and nonseminoma. The nonseminoma germ cell tumors include: embryonal **carcinoma**, malignant teratoma, endodermal sinus tumor, choriocarcinoma, and mixed germ cell tumors. The specific category of extragonadal germ cell tumor that is present has a major influence on both treatment and prognosis.

Demographics

Extragonadal germ cell tumors are quite rare. One new case is diagnosed annually for every 1 million people in the United States.

In young children, extragonadal germ cell tumors tend to occur primarily in the presacral area. The majority of these tumors are benign.

In adults, extragonadal germ cell tumors tend to be in the mediastinum. Of these, approximately 40% are malignant.

Malignant extragonadal germ cell tumors occur with equal frequency in boys and girls. But, they are approximately nine times more likely to occur in men than in women.

Extragonadal germ cell tumors occur with equal frequency in members of all races and ethnic groups. There does not appear to be any relationship of extragonadal germ cell tumors to any geographic region.

KEY TERMS

Germ cells—Cells that are involved in reproduction. These cells are usually located in the gonads. Sometimes they fail to move to the gonads during embryonic development and cause tumors in other parts of the body.

Gonads—The reproductive organs: the testes and ovaries.

Mediastinum—The mid-chest area between the lungs.

Pineal gland—A pea-sized gland just below the brain.

Presacral area—The lowest part of the back.

Causes and symptoms

The cause, or causes, of extragonadal germ cell tumors are not known.

The symptoms of an extragonadal germ cell tumor depend on the type and location of the tumor.

Mediastinum

Germ cell tumors of the mediastinum are primarily diagnosed in men between the ages of 20 and 30. Symptoms include:

- chest pain
- breathing problems
- cough
- fever

Presacral area

Presacral germ cell tumors are primarily diagnosed in children under the age of six. These are generally seen as a mass in the lower abdomen or buttocks. Because of the size and location of the tumor, the patient may have difficulty passing urine or having a bowel movement. Tumors detected in children under the age of six months are benign in 98% of cases. Tumors detected in children over the age of six months are malignant in approximately 65% of cases.

Pineal area

Almost all pineal germ cell tumors occur in people under the age of 40. Symptoms include:

- headache
- nausea
- vomiting
- lethargy
- difficulty walking
- memory loss
- an inability to look upward
- uncontrolled eye movement
- double vision

In some cases, a pineal germ cell tumor can begin to produce hormones that can cause a child to enter puberty at an abnormally young age (precocious puberty).

Diagnosis

The diagnosis of an extragonadal germ cell tumor usually begins with a thorough physical examination. In cases where a presacral tumor is suspected, this will include a rectal examination and a pelvic examination in women. In cases where a germ cell tumor of the pineal area is suspected, a complete neurological examination will be performed.

Mediastinum

The first test for a tumor of the mediastinum is a standard chest **x ray**. This will detect the tumor and show its location in 95% of cases. This will be followed by a computed tomography (CT) scan of the chest to determine the size of the tumor and by a CT scan of the abdomen to see if there has been a spread (**metastasis**) to the liver or other abdominal sites.

Diagnosis is generally confirmed by taking a needle **biopsy** of the tumor. In this procedure, a needle is injected directly into the tumor and a sample is removed.

Certain types of nonseminomas can be detected via blood tests for levels of alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-hCG).

Presacral area

Germ cell tumors of the presacral area are diagnosed by either **magnetic resonance imaging** (MRI) or ultrasound imaging techniques. These techniques allow for the determination of both the location and the precise size of the tumor. To check for metastases, a bone scan, chest x rays, and a CT scan of the lungs should be performed. Sometimes a bone marrow biopsy is also ordered.

Diagnosis of a presacral germ cell tumor is confirmed by a direct biopsy of the tumor. This may be either an excisional biopsy, in which the tumor is first removed, then examined; or, a needle biopsy, in which only a sample of the tumor is removed for examination.

Pineal area

A CT scan of the head will usually show a pineal tumor. An MRI scan, using gadolinium as a tracer chemical, may also be ordered.

Blood tests for AFP and beta-hCG may help to diagnose pineal area germ cell tumors. Tests for these chemicals on the cerebrospinal fluid (spinal tap or lumbar puncture) may also be ordered.

The diagnosis of a pineal area germ cell tumor is usually confirmed upon biopsy of the tumor after it has been removed from the patient.

Treatment team

Treatment of an extragonadal germ cell tumor depends on the location of the tumor. Most tumors are treated with a combination of surgery, **chemotherapy**, and radiation treatments.

Germ cell tumors of the mediastinum are generally not surgically removed. They are treated with high-dose radiation and sometimes with chemotherapy. Germ cell tumors of the presacral area are treated with chemotherapy to shrink the tumor, then surgery to remove the tumor. This surgery is generally performed by a physician who specializes in tumor removal surgery of the lower abdomen and pelvis. Germ cell tumors of the pineal area are generally removed by a brain surgeon and then the patient is treated with radiation and/or chemotherapy.

Chemotherapy is administered under the direction of a physician who specializes in cancer (oncologist). Radiation therapies are generally administered by radiological technicians under the direction of an oncologist, a radiologist, a health physicist, and/or a medical radiation dosimetrist.

QUESTIONS TO ASK THE DOCTOR

- Which type of extragonadal germ cell tumor do I have?
- Is my tumor operable?
- What are my treatment options?
- What is the likelihood of my type of tumor being successfully removed with a single surgery?
- What is the prognosis for my tumor type?
- How often should I seek follow-up examinations?

Clinical staging, treatments, and prognosis

The prognosis for patients with benign extragonadal germ cell tumors is excellent after surgery to remove the tumor is completed.

In the cases of malignant extragonadal germ cell tumors, the prognosis depends on the type and size of the tumor that is found.

Fifty-six percent of nonseminomas and 90% of seminomas have a good prognosis. Another 28% of nonseminomas and the remaining 10% of seminomas have an intermediate prognosis. While 16% of nonseminomas have a poor prognosis. A good prognosis is defined as a five-year survival rate above 85%. An intermediate prognosis is defined as a five-year survival rate between 50% and 85%. A poor prognosis is defined as a five year survival rate lower than 50%.

For both seminomas and nonseminomas, the prognosis is better if the tumors have not metastasized to other tissues. This is particularly true in the case of **mediastinal tumors**: those that have metastasized outside the general region of the lungs lead to particularly poor prognoses.

The prognosis for nonseminomas is based primarily on AFP and hCG concentrations found in the blood. The lower the levels of these two chemicals in the blood, the better the prognosis.

Alternative and complementary therapies

There are no effective alternative treatments for extragonadal germ cell tumors other than surgery, chemotherapy, and radiation.

Coping with cancer treatment

Most patients who undergo surgery to remove their tumors can resume their normal activities within a few days of the operation.

In some cases of presacral area germ cell tumors, it is difficult to remove the entire tumor in a single operation. In these cases, it is necessary for the patient to undergo a second course of chemotherapy prior to a second surgery to remove the remaining tumor.

When extensive chemotherapy is necessary, the patient may require counseling to help cope with the side effects of these treatments, such as loss of head and body hair, **weight loss**, nausea, **fatigue**, and changes in psychological well-being.

Clinical trials

There were 12 **clinical trials** underway, in early 2001, aimed at the treatment of extragonadal germ cell tumors. More information on these trials, including contact information, may be found by conducting a clinical trial search at the web site of the National Cancer Institute, CancerNet (<http://cancernet.nci.nih.gov>).

Prevention

Because the causes of extragonadal germ cell tumors are not known, there are no known preventions.

Special concerns

Repeat surgery may be necessary for extragonadal germ cell tumors, particularly those of the presacral area because these tumors are often difficult to remove completely. Careful monitoring by the medical team will be required.

See also Bone marrow aspiration and biopsy; Nuclear medicine scan; Testicular cancer.

Resources

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F

Famciclovir *see* **Antiviral therapy**

Familial cancer syndromes

Definition

Familial cancer syndrome is a genetic condition that causes an increased risk for specific types of cancers. Familial cancer syndromes account for only 5–10% of all cancers.

Description

Most cancer is not inherited. Cancer is common; in 2004, more than 1.3 million new cancer cases were diagnosed. Many people have relatives who have had cancer, but most of the time this is due to chance or environmental factors. In a familial cancer syndrome, an inherited genetic mutation causes a person to be at increased risk for cancer and other physical symptoms. There are many different familial cancer syndromes, and each one has a specific set of characteristic cancers and physical symptoms associated with it. For example, BRCA1 and BRCA2 gene mutations are associated with an increased risk for breast and **ovarian cancer**. Examples of other familial cancer syndromes include **von Hippel-Lindau syndrome**, **Peutz-Jeghers syndrome**, and **Li-Fraumeni syndrome**.

Features

Below is a list of "clues" in a family tree that make a familial cancer syndrome more suspicious:

- Two or more close relatives with the same type of cancer (on the same side of the family).
- Cancer diagnosed at an earlier age than usual.
- Cancer diagnosed more than once in the same person (more than one primary cancer, not a cancer recurrence).
- Cluster of cancers associated with a known familial cancer syndrome (such as breast and ovarian).
- Many cases of cancer in a family, more than can be accounted for by chance.
- Cancer in a person who also has birth defects.
- Evidence of autosomal dominant inheritance, which is when a gene from one parent overrides that of the other parent. When one parent has a dominant abnormal gene, offspring each have a 50% chance of inheriting that gene.

Diagnosis

The most important step in determining if a family has a familial cancer syndrome is gathering an accurate family history. The family history should include children, brothers and sisters, parents, aunts, uncles, grandparents, nieces, nephews, and cousins on both sides of the family. For a person who has had cancer, the type of cancer and age at diagnosis should be listed for each cancer. It may be necessary to obtain medical records to confirm what type of cancer a person had since family members may not always be aware of specific information. Birth defects, unusual skin findings, benign tumors, and special screening tests (such as **colonoscopy** to look for colon polyps) should also be noted. When this type of family information is unavailable, it may be possible to look for clues in one or a small number of family members. Many hospitals have a "familial cancer clinic," which is a team of health professionals with expertise in familial cancer syndromes. Geneticists, genetic counselors, oncologists, and social workers assist individuals and families by providing risk assessment, support, screening and prevention recommendations, and **genetic testing** options (if available).

Inheritance

Some familial cancer syndromes show autosomal dominant inheritance, which means that an affected person has a 50% chance of passing on the genetic mutation

Suppressor genes that, when deleted, predispose families to cancers

Gene	Consequence of gene loss
Rb	Retinoblastoma and osteosarcoma
TP53	Li-Fraumeni syndrome
Wt1	Wilms' tumor
VHL	von Hippel-Lindau syndrome; renal cell carcinoma
NF1	Von Recklinghausen's disease; neurofibromatosis type 1; schwannoma and glioma
NF2	Neurofibromatosis type 2; acoustic neuroma and meningiomas
APC	Familial adenomatous polyposis; colorectal tumors

to each of his or her children. Other familial cancer syndromes show autosomal recessive inheritance, which means that both parents are usually not affected, but are carriers of a mutation for the condition. In autosomal recessive inheritance, each child born to parents who are carriers has a 25% chance of having the condition. When a person is diagnosed with a familial cancer syndrome, relatives should be examined for signs of the syndrome. Sometimes a person identified as having a familial cancer syndrome is the first person in the family to be affected. That person is able to pass the condition on to his or her children, but the parents and siblings are not affected. Depending on the syndrome, genetics professionals can determine who in the family is at risk.

Risks

Different familial cancer syndromes have different risks for cancer and associated symptoms. In general, a person who inherits the syndrome has a higher risk of developing the cancer associated with the syndrome than the general population, but this is not a guarantee that cancer will ever develop. On the other hand, someone who does not inherit the syndrome is not at increased risk for cancer above that of the general population, but this is no guarantee that cancer will not develop, and screening guidelines for the general population should be followed.

Genetic Testing

Although genetic testing is available for many familial cancer syndromes, there are genes that have yet to be discovered. Each syndrome has special issues surrounding genetic testing; for example, what age should the test be done? How would the results change medical management? Does insurance cover the test? How will the information affect the family? Health professionals familiar with familial cancer syndromes keep up to date with advances in **cancer genetics**, and work with families to discuss the risks, benefits and limitations of genetic testing.

KEY TERMS

Gene—A unit of heredity that codes for the formation of a protein. Genes determine how we grow and develop.

Inherited—Qualities that are transmitted from parent to offspring in the genes.

Mutation—A change in a genetic code which may result in altered function of a gene.

Syndrome—The clustering of signs and symptoms that characterize a disease.

The Human Genome Project

Since mid-2002, when the first complete draft of the Human Genome Project was completed, rapid advances have been made in the discovery of specific locations of cancer genes. For example, late in 2003, scientists tracked down the exact chromosome that carries certain familial forms of colorectal cancer. By mapping every normal gene in the human body, scientists can compare abnormal DNA sequences that lead to cancer. For example, the BRAF mutation has been linked to several cancers. Data from the Human Genome Project will help identify cancer genes, develop better genetic tests for cancer, and lead to improved preventive and therapeutic interventions.

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Famotidine *see* **Histamine 2 antagonists**

Fanconi anemia

Definition

Fanconi anemia is an inherited form of aplastic anemia characterized by an abnormally low number of cellular components in the blood due to failing bone marrow.

Description

Fanconi anemia (FA) is a rare genetic disease caused by mutations or alterations in one of seven different genes. The disease is an autosomal recessive condition, meaning that the genes are not located on the sex chromosomes and a mutated gene copy must be inherited from both parents in order for a person to be affected. Test results of cells from FA patients suggest that the genetic defects of FA reduce the cell's ability to repair damaged deoxyribonucleic acid (DNA), the primary chemical component of chromosomes. Five of the seven genes associated with FA have been isolated.

Demographics

With only approximately 1000 cases documented in the literature, FA is a rare disease with varied frequency in different ethnic groups. It is particularly prevalent in the Ashkenazi Jewish population, where carriers are 1 in 89 persons, compared to an overall carrier frequency of 1 in 100 to 600. A carrier is a person unaffected by the disease who has one mutated and one normal gene in their genome. Both parents must be carriers in order to produce a child with FA.

Causes and symptoms

FA is caused by inheriting two abnormal copies of one of seven different genes, all thought to be involved in DNA repair. About 67% of children with FA are born with some sort of congenital defect. The problems seen include:

- short stature
- abnormalities of the thumb or arm
- other skeletal abnormalities such as of the hip or ribs
- kidney malformations
- skin discoloration
- small eyes or head
- mental retardation
- low birth weight and failure to thrive
- abnormalities of the digestive system
- heart defects

The defining characteristic of FA is progressive pancytopenia, a gradual reduction of the cellular components of the blood. A reduction in red blood cells is typically noted first, then white blood cells, and finally, platelets. Complete bone marrow failure in FA patients is usually seen between the ages of three and twelve, with a median of seven.

Later in life, FA patients have delayed sexual maturity and an increased probability of developing cancer. For FA patients surviving into adulthood, 50% develop leukemia (a malignancy of the white blood cells) and/or myelodysplastic syndrome (MDS, a pre-leukemic state). Persons with FA also have an elevated chance of developing squamous cell cancers (originating in the outer layer of the skin), particularly gynecological cancers (for females); head, neck and throat cancers; **gastrointestinal cancers**; and liver cancers.

Diagnosis

Diagnosis can be made upon the appearance of the characteristic congenital defects, but is more common upon development of aplastic anemia (when the bone marrow fails to produce normal numbers of blood cells). Definitive diagnosis involves a showing of an unusual level of chromosome breakage when cells are exposed to DNA damaging agents. Additionally, with five of the seven genes associated with FA isolated, genetic engineering techniques can often be used to determine exactly what gene mutation is responsible for the disease. An estimated 90% of FA patients have mutations within the FANCA, FANCC and FANCG genes, all of which have been isolated.

Treatment team

FA is usually treated by pediatricians, hematologists, and, if a bone marrow transplant (BMT) is performed, a specialized teams of physicians, nurses, and medical assistants who are experienced in BMT.

Clinical staging, treatments, and prognosis

There is no clinical staging system for FA.

BMT and androgen therapy are two long-term non-experimental treatments for FA. BMT involves the

KEY TERMS

Aplastic anemia—A disease in which the bone marrow stops producing all three types of cells of the blood: red blood cells, white blood cells, and platelets.

Fludarabine—A drug that inhibits a blood cell's ability to produce DNA, eliminating native cells from FA patients so they can undergo BMT.

Myelodysplastic syndrome—A disease where the bone marrow stops producing healthy blood cells and the cells that are produced function poorly. This syndrome sometimes develops into leukemia.

Neutrophil—A type of white blood cells important in the defense of the body against infection.

QUESTIONS TO ASK THE DOCTOR

- Which FA gene is responsible for my child's illness?
- Are growth factor or gene therapies appropriate for my child?
- When should bone marrow transplantation be considered as an appropriate treatment?

suppression of the patient's own marrow and replacement with stem cells of the donor. The effectiveness of BMT is highly dependent on the existence of a donor that is closely matched to the patient. For sibling match (full match) transplants, the two-year survival rate is about 80%, compared to about 37% for less than a full match. The difference is due the prevalence of graft versus host disease (GVHD), where the recipient's body rejects the donor cells. The use of T-cell (a type of immune cell) depletion before transplantation and the drug **fludarabine** have significantly reduced the occurrence of GVHD. BMT does not alter the tendency of FA patients to develop other malignancies later in life, however.

Androgen therapy involves the administration of male hormones to stimulate the production of blood cells. Most FA patients respond for at least a time to this therapy. The cell increase lasts a few years at most, however, and the hormones have serious side effects, including masculinization of female patients and liver disease.

Clinical trials

Growth factor therapy and gene therapy are two treatments being tested in **clinical trials**. Two growth factors—granulocyte/macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF)—were shown to increase blood cell production. Patients with low neutrophil counts particularly benefit from this treatment.

A clinical trial for gene therapy of FA patients is ongoing. The normal copy of the mutated gene is introduced into the patient's own bone marrow stem cells using a viral vector. When the virus infects the stem cells, the normal FANC gene is integrated into the stem cell's DNA. This therapy will, theoretically, correct the defect in the stem cells and prevent their premature death, curing the aplastic anemia seen in FA patients. As with BMT, however, this gene therapy will not reduce the development of other cancers in FA patients.

Prevention

The only known method of prevention of this disease is prenatal diagnosis and termination of pregnancies for affected embryos. Preimplantation genetic diagnosis, where one or two cells are tested from *in vitro* fertilized embryos, is also available. This method avoids the need for abortion, but carries more risk.

Special concerns

Because FA can be present without any outward symptoms, it is essential that any potential sibling donor for BMT be carefully tested for the disease using white blood cell exposure to DNA damaging agents or direct examination of their FANC gene copies before the transplant.

See also Bone marrow transplantation; Genetic testing.

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Fatigue

Description

Fatigue is a feeling of exhaustion or loss of strength. The duration of fatigue for a patient with cancer has been found to last from one to two times the length of time between diagnosis and completion of treatment, so it is common for fatigue to persist beyond a patient's treatment regimen.

Causes

Many people experience fatigue as a side effect of cancer treatment. Both **chemotherapy** and radiation therapy are associated with fatigue. Scientists believe fatigue also occurs because the body is devoting so much of its energy fighting the cancer that it has little left over for daily life. Often the feelings of exhaustion are more intense immediately following a cancer treatment, but they gradually ease over time as the body gains strength.

During chemotherapy, anti-cancer drugs kill both cancer cells and healthy cells, including red blood cells. This can lead to **anemia**, or low red blood cell counts, which causes fatigue. Chemotherapy agents also attack white blood cells, weakening the immune system.

Medications, pain, **depression**, and the stress of the diagnosis and treatment are other factors that result in fatigue.

Treatments

If anemia is a problem, physicians may prescribe iron supplements or drugs, such as **erythropoietin**, to stimulate blood cell growth. In some cases, blood transfusions may be necessary.

KEY TERMS

Anemia—A condition that occurs when the body has low red blood cell counts. It can cause fatigue.

Erythropoietin—A drug used to stimulate blood cell growth when a person has anemia.

Many people with cancer find that they must pace themselves, alternating periods of activity with small naps. Going to bed earlier also seems to help.

Research has shown that people who exercise experience less cancer-related fatigue. Walking or using an exercise bicycle are good choices. For those who have severe weakness, even a few minutes of gentle stretching in bed can make a difference.

Eating nutritious food is another way to get an energy boost to better fight cancer. Include a variety of fruits and vegetables, whole grains and plenty of protein, if **nausea and vomiting** are not a problem. High-calorie liquid meals can help offset severe **weight loss** for those who cannot tolerate solid foods. Drinking plenty of water also helps prevent **diarrhea** and dehydration, which add to fatigue.

Alternative and complementary therapies

Yoga has proven to be highly effective in reducing stress, thereby increasing energy and helping people to relax and sleep better.

Marijuana has been used to help ease nausea in cancer patients. Since a loss of appetite can cause weakness and fatigue, marijuana may help indirectly. Most states do not permit the use of marijuana for medical reasons. Physicians will be aware of these regulations.

Other complementary therapies, such as massage, aromatherapy, meditation, or prayer, help people with cancer relax, easing their worries and ultimately combatting fatigue.

See also Complementary cancer therapies.

Resources

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Fecal occult blood test

Definition

The fecal occult blood test (FOBT) is performed as part of the routine physical examination during the examination of the rectum. It is used to detect microscopic blood in the stool and is a screening tool for colorectal cancer.

Purpose

FOBT uses chemical indicators on stool samples to detect the presence of blood not otherwise visible. (The word "occult" in the test's name means that the blood is hidden from view.) Blood originating from or passing through the gastrointestinal tract can signal many conditions requiring further diagnostic procedures and, possibly, medical treatment. These conditions may be benign or malignant and some of them include:

- colon, rectal, and gastric (stomach) cancers
- ulcers
- hemorrhoids
- polyps
- inflammatory bowel disease
- irritations or lesions of the gastrointestinal tract caused by medications (such as nonsteroidal anti-inflammatory drugs, also called NSAIDs)
- irritations or lesions of the gastrointestinal tract caused by stomach acid disorders, such as reflux esophagitis

The FOBT is used routinely (in conjunction with a rectal examination performed by a physician) to screen for colorectal cancer, particularly after age 50. The ordering of this test should not be taken as an indication that cancer is suspected. The FOBT must be combined with regular screening endoscopy (such as a **sigmoidoscopy**) to detect cancers at an early stage.

Precautions

Certain foods and medicines can influence the test results. Some fruits contain chemicals that prevent the guaiac, the chemical in which the test paper is soaked, from reacting with the blood. Aspirin and some NSAIDs irritate the stomach, resulting in bleeding, and should be avoided prior to the examination. Red meat and many vegetables and fruits containing vitamin C also should be avoided for a specified period of time prior to the test. All of these factors could result in a false-positive result.

Description

Feces for the stool samples is obtained either by the physician at the rectal examination or by the patient at home, using a small spatula or a collection device. In most cases, the collection of stool samples can easily be done at home, using a kit supplied by the physician. The standard kit contains a specially prepared card on which a small sample of stool will be spread, using a stick provided in the kit. The sample is placed in a special envelope and either mailed or brought in for analysis. When the physician applies hydrogen peroxide to the back of the sample, the paper will turn blue if an abnormal amount of blood is present.

Types of fecal occult blood tests

Hemoccult is the most commonly used fecal occult blood test. The Hemoccult test takes less than five minutes to perform and may be performed in the physician's office or in the laboratory. The Hemoccult blood test can detect bleeding from the colon as low as 0.5 mg per day.

Tests that use anti-hemoglobin antibodies (or immunochemical tests) to detect blood in the stool are also used. Immunochemical tests can detect up to 0.7 mg of hemoglobin in the stool and do not require dietary restrictions. Immunochemical tests

- are not accurate for screening for stomach cancer
- are more sensitive than Hemoccult tests in detecting colorectal cancer
- are more expensive than Hemoccult tests

KEY TERMS

Occult—Not visible or easily detected.

Hemoquant, another fecal occult blood test, is used to detect as much as 500 mg/g of blood in the stool. Like the Hemoccult, the Hemoquant test is affected by red meat. It is not affected by chemicals in vegetables.

Fecal blood may also be measured by the amount of chromium in the red blood cells in the feces. The stool is collected for three to ten days. The test is used in cases where the exact amount of blood loss is required. It is the only test that can exclude blood loss from the gastrointestinal area with accuracy.

Medicare coverage began on January 1, 2004, for a newer fecal occult blood test based on immunoassay. This technique does not rely on guiaic, so it is not influenced by diet or medications used prior to the test. The immunoassay test also requires fewer specimen collections. At a conference of gastroenterologists (physicians who specialize in diseases of the stomach and related digestive systems), a company announced a new fecal occult blood test that was based on DNA and appeared more sensitive than traditional tests. Widespread use of these new tests remains to be seen; the traditional guiaic test has been in place for about 30 years.

Preparation

For 72 hours prior to collecting samples, patients should avoid red meats, NSAIDs (including aspirin), antacids, steroids, iron supplements, and vitamin C, including citrus fruits and other foods containing large amounts of vitamin C. Foods like uncooked broccoli, uncooked turnips, cauliflower, uncooked cantaloupe, uncooked radish and horseradish and parsnips should be avoided and not eaten during the 72 hours prior to the examination. Fish, chicken, pork, fruits (other than melons) and many cooked vegetables are permitted in the diet.

Results

Many factors can result in false-positive and false-negative findings.

Positive results

It is important to note that a true-positive finding only signifies the presence of blood—it is not an indication of cancer. The National Cancer Institute states that, in its experience, less than 10% of all positive results were caused by cancer. The FOBT is positive in 1%–5% of the unscreened population and 2%–10% of those are found to have cancer. The physician will want to follow up on a positive result with further tests, as indicated by other factors in the patient's history or condition.

QUESTIONS TO ASK THE DOCTOR

- What kinds of foods should I avoid prior to the FOBT?
- How much stool should I collect for the stool samples?
- What is the next step if my test is postive?

Negative results

Alternatively, a negative result (meaning no blood was detected) does not guarantee the absence of **colon cancer**, which may bleed only occasionally or not at all. (Only 50% of colon cancers are FOBT-positive.)

Conclusions

Screening using the FOBT has been demonstrated to reduce colorectal cancer. However, because only half of colorectal cancers are FOBT-positive, FOBT must be combined with regular screening endoscopy to increase the detection of pre-malignant colorectal polyps and cancers.

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Fentanyl *see* **Opioids**

Fentanyl transdermal *see* **Fentanyl**

Fertility issues

Overview

Any procedure or medication that interferes with the functioning of the testes or ovaries affects fertility. The choices made before cancer treatment begins can determine whether the patient will remain fertile after treatment. Prior to deciding on a treatment plan, it is important for the patient to discuss the issue of fertility with the treatment team so that all options, with their associated risks, can be considered.

Conventional cancer treatments and their effects on fertility

Cancer is usually treated with surgery, **chemotherapy**, and/or radiation, with the type and stage of the cancer dictating the treatment regimen recommended. While some physicians may routinely take into consideration alternatives to spare a patient's fertility, others may not, feeling that to differ from the treatment norm may compromise the patient's best chances for survival. Patients for whom fertility preservation is important, or for whom fertility-sparing measures could compromise treatment outcome, must discuss this issue fully with their treatment team.

Surgery

Surgery for cancer usually involves removal of the cancerous area, with some sampling of the adjacent area and lymph nodes to check for **metastasis**. If surgery must involve the removal of both of the testes or ovaries, the man will not be able to provide his own sperm, and the woman her own egg, towards the development of a biologic child. (A couple may be able to use donated sperm or egg when attempting a future pregnancy, however.) Fertility-sparing surgery may be an option for some individuals, depending on the type and stage of their cancer. For example, a woman with **ovarian cancer** contained to one ovary may be able to have just that one removed. The same is true for a man with **testicular cancer** contained to one testicle. In the case of testicular cancer, removal of retroperitoneal lymph nodes during surgery may damage the nerves affecting ejaculation. Men may wish to discuss nerve-sparing surgery and their concerns for fertility with their surgeon prior to surgery.

Chemotherapy

Chemotherapy affects the whole body, but certain drugs are less harmful to the reproductive tract than others. The drugs used in chemotherapy are highly toxic, in order to kill any cancer cell. However, they are not very selective, meaning that in addition to cancerous cells, normal cells are killed as well. It may take a few years after chemotherapy has finished to understand its temporary or permanent effect on fertility. It is generally recommended that women wait about two years after chemotherapy before attempting to become pregnant, to avoid the risk of a pregnancy that may end in miscarriage or a fetal malformation. Men who have had chemotherapy can have their sperm analyzed after treatment has finished to check sperm counts and motility.

There is a concern that individuals may delay treatment in order to undergo various fertility-preserving measures, such as sperm banking or egg retrieval and cryopreservation, and that this delay could result in a poorer treatment outcome. Some women undergo attempts at egg retrieval and embryo cryopreservation after an initial dose of chemotherapy. Some treatment centers offer the option of doing the chemotherapy in stages. The first stage of chemotherapy uses medications that are considered less toxic. Then the more intensive treatment follows after the harvesting of egg or sperm. However, it is still not yet clear what kind of damage may have been endured by tissue harvested right after some chemotherapy.

Radiation

Radiation is known to damage the highly sensitive sperm and eggs. Just as chemotherapy attacks healthy

KEY TERMS

Cryopreservation—The process of freezing sperm, ova, or embryos to preserve them for future use.

Oocyte retrieval—The process of obtaining eggs from a woman's ovary for future reproduction.

Sperm banking—Sperm banking is a process of freezing, or cryopreserving, sperm for use in the future. The sperm may be obtained via ejaculation, or by aspiration. The process of sperm banking may take one to two weeks to complete. The method of aspirating the sperm directly from the testicle is called testicular semen aspiration.

Treatment team—An interdisciplinary group of professionals whose focus is to collaborate on and coordinate the care of the patient. For the cancer patient this team might be comprised of a surgeon, oncologist, radiologist, gynecologic oncologist, urologic oncologist, nurse specialists, and social workers.

cells, so does radiation. However, radiation technology is able to focus very tightly on the cancerous area, which decreases risk to healthy tissue. When radiation for cancer does not involve the pelvic area, it may be possible to successfully shield the reproductive organs to preserve fertility. If the area needing irradiation is the pelvis, the reproductive organs are at great risk of damage.

When radiation is done to the pelvic area, women often experience a pause in menstruation, along with other symptoms of menopause. There may also be vaginal dryness, **itching**, and burning. Radiation may affect sexual desire as well. Men may experience a decrease in sperm count and motility, and difficulty in having or maintaining an erection. These changes may be temporary or permanent, and it may take up to a few years to determine if the effects were temporary or permanent. Sperm banking or cryopreservation of eggs may allow the individual reproductive success in the future.

Since radiation can be harmful to the fetus, pregnancy during **radiation therapy** is contraindicated, and because the full effect of the radiation on fertility cannot be predicted, individuals should use contraception during sexual relations while receiving radiation therapy.

Bone marrow transplant

A bone marrow transplant (BMT) may be part of the suggested treatment regimen. If so, patients need to understand its potential impact on future fertility. While the actual BMT does not jeopardize fertility, chemotherapy or radiation done prior to the BMT in preparation for the body's receiving of the new marrow can damage fertility. This pretreatment can destroy cells in the reproductive organs, rendering the individual infertile. While each case is unique, patients may wish to discuss the impact of their treatment on their reproductive future, and consider sperm banking or egg cryopreservation.

Children's cancers and future fertility

In the case of children, chemotherapy and radiation for childhood cancer can cause permanent damage to the ovaries or testes. In boys who have become sexually mature, sperm banking may provide future reproductive options. Options such as sperm aspiration, and cryopreservation of female ova are still considered experimental in children. While they may be effective, researchers are concerned that parents and their children may be unrealistic in their hopes for future fertility, and that the reintroduction of the harvested tissue may return latent cancer cells into the body. While research may bring new options, obtaining true informed consent involving children and their parents is an issue of moral and practical concern.

Alternative and complementary therapies

Individuals undergoing cancer treatment may turn to alternative therapies for a number of reasons. Techniques such as meditation, therapeutic touch, yoga, t'ai chi, and guided imagery can be very helpful in reducing stress and its effects on the body. Acupuncture has been shown through research studies to be effective in reducing the **nausea and vomiting** associated with chemotherapy. However, a study reported in the March 1999 issue of the medical journal *Fertility and Sterility* investigated several herbal remedies and their effect on sperm and ova. While this study was involved in animal research, the finding that high concentrations of St. John's wort, an herbal supplement used for mild to moderate **depression**, Echinacea, and ginkgo biloba damaged reproductive cells raises concern for its effect on humans. In particular, St. John's wort was found to be mutagenic to sperm cells.

Special concerns

Some cancers, such as testicular cancer, affect primarily young men. Most men diagnosed with testicular cancer are between the ages of 15 and 40. Sperm banking is highly recommended for these men. The method intracytoplasmic sperm injection uses just one sperm to fertilize one egg, by injecting the sperm directly into the egg. This can result in a fertilized egg for insemination, even when the sperm has decreased motility. It has a success rate of 30%.

QUESTIONS TO ASK THE DOCTOR

- What is the type and stage of my cancer?
- What treatment options do I have that would retain my fertility?
- Is my survival compromised if I choose fertility-sparing treatment?
- Would the health of future child/children be compromised if I undergo this treatment?
- Can you provide me with research studies of others who had this treatment and went on to have children?
- How long should I wait after treatment before attempting a pregnancy?
- If treatment is successful, what can I expect in terms of survival and quality of life?
- If treatment is unsuccessful, what can I expect in terms of survival and quality of life?
- What is the type and stage of my child's cancer?
- Does the treatment of this cancer have a risk of developing another cancer later on?
- How will this treatment affect my child's development during puberty?
- What effect will this treatment have on my child's future fertility?

Fertility issues and the development of cancer

Fertility issues can also play a role in the development of cancer. For example, women having their first child after 30 are at slightly higher risk of developing ovarian cancer than those having their first child before age 30. The number of ovulatory cycles a woman experiences also appears to affect her risk for ovarian cancer. A longer reproductive period (early menarche and late menopause) appears to raise the risk, while having children (there is no ovulation during pregnancy), breastfeeding (there is some suppression of ovulation during breastfeeding), and the use of oral contraceptives for at least five years decreases the risk.

Women who used the infertility medication clomiphene citrate without becoming pregnant were found in some studies to have a greater risk of developing a low malignancy potential ovarian cancer. In a November 1999 issue of the medical journal *Lancet*, researchers reported that women whose infertility remained unexplained were found to have more ovarian and uterine cancers, irrespective of whether or not they had been treated for the infertility. Also, more breast cancers were detected in the first year after treatment for infertility terminated than was expected. The lead author of the study speculated that these cancer diagnoses may be due to closer medical supervision that resulted in early detection. In some cases it was believed that the infertility was a symptom of the undiagnosed cancer.

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Fever

Description

Normal body temperature varies somewhat from one individual to another but displays a general range and pattern around the "normal" temperature of 98.6°F. Early morning body temperature may be as low as 97°F, and as high as 99.3°F in the afternoon hours yet still be considered normal. Higher temperatures may be observed in healthy people, but an abnormal elevation (pyrexia) is classified as **hyperthermia**, or fever. Fever results from a failure in the body's ability to regulate and dissipate heat. Any fever presents an unpleasant and uncomfortable state for the patient. Fever may cause the patient to experience **fatigue**, chills, sweats, nausea, and—in some cases—life-threatening conditions. When fevers occur in the elderly or the very young, the effects can be more harmful than in individuals who fall between those two age groups. The elderly may experience poor blood circulation, heart failure, an irregular heartbeat, or mental episodes. Children may lapse into fever-induced seizures. It is possible to treat fever with lukewarm sponge baths or bathing, removing excess clothing or bedding, and increasing the patient's fluid

intake; however an important treatment is medication that lowers the body temperature to its normal range.

Causes

Fever associated with cancer can generally be categorized into four major causal groups: infection, tumors, allergic reactions to a drug, or allergic reaction to blood components in transfusion therapies. For cancer patients, fever should be considered a result of infection until an alternative cause is diagnosed. When a fever develops in a cancer patient, the individual must be thoroughly examined to determine the cause. A comprehensive physical examination should be administered by the physician and blood drawn for laboratory analysis.

Once a diagnosis has been made and treatment initiated, it is important to address problems created by the fever itself. It may be necessary to increase fluids and nutritional supplements. Because fever places increased demands on the body, this can be critical in restoring normal health for patients who may already be nutritionally compromised. Fever in a patient with **neutropenia** (low white blood cell count) represents the potential for a critical, life-threatening situation, and treatment should begin as quickly as the patient can reach the emergency room.

Physicians do not fully understand how tumors can cause fever, but certain correlations are well documented. Fever spikes may indicate that a tumor has grown or spread to other areas of the body, or that the tumor has produced some type of blockage. The fever associated with a tumor tends to be cyclic, and subsides with tumor treatment and recurs when the tumor returns or increases in size. In the case of drug-associated fever, the fever is an allergic-type reaction to a particular medication or combination of medications. Similarly, an **immune response** to donor blood cells is the typical cause of fever associated with blood components.

Treatments

Each of the major causes for fever associated with cancer has recommended conventional treatment procedures. For infection-related fever, broad-spectrum **antibiotics**, given orally, rectally, or intravenously, are the principle method of control. Some antibiotics may be started before a definitive diagnosis is made to retard additional complications caused by the infection. Treatment typically is administered for five to seven days as long as the fever and infection show a positive response.

Fever from a tumor is best treated by treating the tumor itself. Supplemental treatment for the fever may include the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Aspirin should only be used in patients with no risk of bleeding problems. The allergic responses manifesting in drug- or blood-associated fever may be treated by various methods: antihistamines and acetaminophen may be administered prior to drug therapy or blood **transfusion therapy**; discontinuing the present drug and choosing alternate medication may be required; blood may require irradiation or removal of white blood cells from the donor blood.

KEY TERMS

Acetaminophen—The generic name for a common nonprescription medication useful in the treatment of mild pain or fever.

Antibiotic—A drug that fights infection.

Antihistamine—A drug that counteracts allergic responses.

Biofeedback—A process by which a person learns to influence two kinds of physiologic responses: those that are not ordinarily under voluntary control; and those that are easily regulated but for which regulation has broken down because of trauma or disease.

Immune response—An alteration in the reactivity of the body's immune system in response to a foreign substance.

Neutropenia—Lowered blood cell counts, especially in white blood cells, chiefly the neutrophils that aid in fighting infection.

Nonsteroidal anti-inflammatory drugs (NSAIDs)—A family of anti-inflammatory drugs that work by inhibiting the production of prostaglandins (a group of compounds that affect diverse bodily processes).

Alternative and complementary therapies

Some patients are investigating and adhering to the use of alternative treatments and complementary therapies. These choices may include holistic healing or herbal medication, and therapy utilizing biofeedback, relaxation therapy, and imagery techniques. Patients maintain that these alternative and complementary therapies add a sense of control to their life during a period when they have little control over anything. No conclusive data exists on the effectiveness of the therapies used alone; however in conjunction with conventional methods of fever management, they do not appear to hinder therapy and may provide the patient increased goodwill and a positive outlook.

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Fibrocystic breast disease *see* **Fibrocystic condition of the breast**

Fibrocystic condition of the breast

Definition

Fibrocystic condition of the breast is a term that may refer to a variety of symptoms: breast lumpiness or tenderness, microscopic breast tissue, and/or the x-ray or ultrasound picture of the breast. It has been called a "wastebasket" diagnosis because a wide range of vaguely defined benign breast conditions may be labeled as fibrocystic condition. It is not a cancer, and the majority of types of fibrocystic conditions do not increase the risk of **breast cancer**.

Description

There is no such thing as a normal or typical female breast. Breasts come in all shapes and sizes, with varying textures from smooth to extremely lumpy. The tissues of the female breast change in response to hormone levels, normal aging, nursing (lactation), weight fluctuations, and injury. To further complicate matters, the breast has several types of tissue; each of these tissue types may respond differently to changes in body chemistry.

Fibrocystic breast condition may be called fibrocystic disease, although it is clearly not a single, specific disease process. Variations or changes in the way the breast feels or looks on **x ray** may cause the condition to be called "fibrocystic change." Other names have been used to refer to this imprecise and ill-defined term: mammary dysplasia, mastopathy, chronic cystic mastitis, indurative mastopathy, mastalgia, lumpy breasts, or physiologic nodularity.

Estimates vary, but 40–90% of all women have some evidence of "fibrocystic" condition, change, or disease. It is most common among women between the ages 30 and 50, but may be seen at other ages.

Causes and symptoms

Fibrocystic condition of the breast refers to technical findings on diagnostic testing (signs); however, this discussion focuses on symptoms that may fall under the general category of the fibrocystic condition. First, a brief review of the structure and function of the breast may be useful.

The breast is not supposed to be a soft, smooth organ. It is actually a type of sweat gland. Milk, the breasts' version of sweat, is secreted when the breast receives appropriate hormonal and environmental stimulation.

The normal breast contains milk glands, with their accompanying ducts, or pipelines, for transporting the milk. These complex structures may not only alter in size, but can increase or decrease in number as needed. Fibrous connective tissue, fatty tissue, nerves, blood and lymph vessels, and lymph nodes, with their different shapes and textures, lie among the ever-changing milk glands. It is no wonder that a woman's breasts may not feel uniform in texture and that the "lumpiness" may wax and wane.

The fibrocystic condition refers to the tenderness, enlargement, and/or changing "lumpiness" that many women encounter just before or during their menstrual periods. At this time, female hormones are preparing the breasts for pregnancy, by stimulating the milk-producing cells, and storing fluid. Each breast may contain as much as three to six teaspoons of excess fluid. Swelling, with increased sensitivity or pain, may result. If pregnancy does not occur, the body reabsorbs the fluid, and the engorgement and discomfort are relieved.

Symptoms of fibrocystic breast condition range from mildly annoying in some women to extremely painful in others. The severity of discomfort may vary from month to month in the same woman. Although sometimes distressing, this experience is the body's normal response to routine hormonal changes.

This cycle of breast sensitivity, pain and/or enlargement, can also result from medications. Some hormone replacement therapies (estrogen and progesterone) used for postmenopausal women can produce these effects. Other medications, primarily, but not exclusively those with hormones may also provoke these symptoms.

Breast pain unrelated to hormone shifts is called "noncyclic" pain. "Trigger-zone breast pain" is a term

that may also be used to describe this area-specific pain. This type of pain may be continuous, or it may be felt intermittently. Trauma, such as a blow to the chest area, a prior breast **biopsy**, or sensitivity to certain medications may also underlie this type of pain. Fibrocystic condition of the breast may be cited as the cause of otherwise unexplained breast pain.

Lumps, apart from those clearly associated with hormone cycles, may also be placed under the heading of fibrocystic condition. These lumps stand out from enlarged general breast tissue. Although noncancerous lumps may occur, the obvious concern with such lumps is cancer.

Noncancerous breast lumps include:

- Adenosis. This condition refers to the enlargement of breast lobules, which contain a greater number of glands than usual. If a group of lobules are found near each other, the affected area may be large enough to be felt.
- Cysts. These are fluid-filled sacs in the breast and probably develop as ducts that become clogged with old cells in the process of normal emptying and filling. Cysts usually feel soft and round or oval. However a cyst deep within the breast may feel hard, as it pushes up against firmer breast tissue. A woman with a cyst may experience pain, especially if it increases in size before her menstrual cycle, as is often the case. Women between the age of 30 and 50 are most likely to develop cysts.
- Epithelial hyperplasia. Also called proliferative breast disease, this condition refers to an overgrowth of cells lining either the ducts or the lobules.
- Fibroadenomas. These are tumors that form in the tissues outside the milk ducts. The cause of fibroadenomas is unknown. They generally feel smooth and firm, with a somewhat rubber-like texture. Typically a fibroadenoma is not attached to surrounding tissue and moves slightly when touched. They are most commonly found in adolescents and women in their early twenties but can occur at any age.
- Fibrosis. Sometimes one area of breast tissue persistently feels thicker or more prominent than the rest of the breast. This feeling may be caused by old hardened scar tissue and/or dead fat tissue as a result of surgery or trauma. Often the cause of this type of breast tissue is unknown.
- Miscellaneous disorders. A number of other benign (noncancerous) breast problems may be placed under the heading of "fibrocystic condition." These problems include disorders that may lead to breast inflammation (mastitis), infection, and/or nipple discharge.

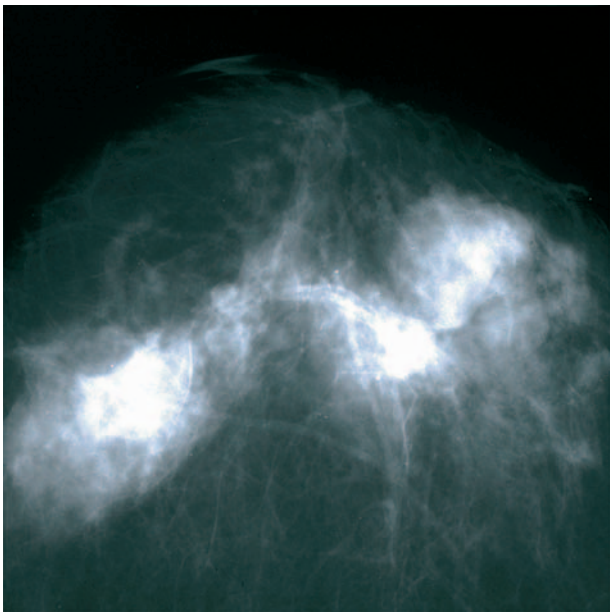
Atypical ductal hyperplasia

The condition known as atypical ductal hyperplasia (ADH) is a condition in which the cells lining the milk ducts of the breast are growing abnormally. This condition may appear as spots of calcium, or calcifications, on the mammogram. A biopsy removed from the breast would confirm the diagnosis. Atypical ductal hyperplasia is not a cancer. In most women, this condition will cause no problems. However, for some women, especially women with family histories of breast cancer, the risk of developing breast cancer is increased. (One study with over 3,000 female participants indicated that about 20% of the participants with atypical hyperplasia and a family history of breast cancer developed breast cancer, as compared to the 8% of participants who developed the disease with atypical hyperplasia and no family history of breast cancer.) For women with ADH and a family history of breast cancer, more frequent mammograms and closer monitoring may be required.

Diagnosis

Breast cancer is the most common concern of women who feel a breast lump or experience an abnormal breast symptom. For peace of mind, and to rule out any possibility of cancer, any newly discovered breast lumps should be brought to the attention of a family physician or an obstetrician-gynecologist. He or she will obtain a history and conduct thorough physical examination of the area. Depending on the findings on physical examination, the patient is usually referred for tests. The most common of these tests include:

- **Mammography**. A mammogram is an x-ray examination of the breasts. The two major types of abnormalities doctors look for are masses and calcifications; either abnormality may be benign or malignant. The size, shape, and edges of these masses help doctors determine whether or not cancer is present. Sometimes, however, this test may be difficult to interpret, however, due to dense breast tissue.
- Ultrasonography. If a suspicious lump is detected during mammography, an ultrasound (the use of high-frequency sound waves to outline the shape of various organs and tissues in the body) is useful (although not definitive) in distinguishing benign from cancerous growths.
- Ductography. A **ductogram** (also called a galactogram) is a test that is sometimes useful in evaluating nipple discharge. A very fine tube is threaded into the opening of the duct onto the nipple. A small amount of dye is injected, outlining the shape of the duct on an x ray, and indicates whether or not there is a mass in the duct.



A mammogram of a female breast indicating multiple cysts. *(Custom Medical Stock Photo. Reproduced by permission.)*

- Biopsy. If a lump cannot be proven benign by mammography and ultrasound, a breast biopsy may be considered. Usually a tissue sample is removed through a needle (fine-needle aspiration biopsy, or FNAB) to obtain a sample of the lump. The sample is examined under the microscope by a pathologist, and a detailed diagnosis regarding the type of benign lesion or cancer is established. In some cases, however, FNAB may not provide a clear diagnosis, and another type of biopsy (such as a surgical biopsy, core-needle biopsy, or other stereotactic biopsy methods—such as the Mammotome or Advanced Breast Biopsy Instrument) may be required.

Other breast conditions such as inflammation or infection are usually recognized on the basis of suspicious history, breastfeeding, or characteristic symptoms such as pain, redness, and swelling. A positive response to appropriate therapies often confirms the diagnosis.

Treatment

Once a specific disorder within the broad category of fibrocystic condition is identified, treatment can be prescribed. There are a number of treatment options for women with a lump that has been diagnosed as benign. If it is not causing a great deal of pain, the growth may be left in the breast. However, some women may choose to have a lump such as a fibroadenoma surgically removed, especially if it is large. Another option to relieve the discomfort of a painful benign lump is to have the cyst suctioned, or drained. If there is any uncertainty regarding diagnosis, the fluid may be sent to the lab for analysis.

KEY TERMS

Advanced Breast Biopsy Instrument (ABBI)—Uses a rotating circular knife and thin heated electrical wire to remove a large cylinder of abnormal breast tissue.

Lobules—A small lobe or subdivision of a lobe (often on a gland) that may be seen on the surface of the gland by bumps or bulges.

Lymph nodes—Rounded, encapsulated bodies consisting of an accumulation of lymphatic tissue.

Mammotome—A method for removing breast biopsies using suction to draw tissue into an opening in the side of a cylinder inserted into the breast tissue. A rotating knife then cuts tissue samples from the rest of the breast; also known as a vacuum-assisted biopsy.

Stereotactic biopsy—A biopsy taken by precisely locating areas of abnormal growth through the use of delicate instruments.

Symptoms of cycle breast sensitivity and engorgement may also be treated with diet, medication, and/or physical modifications. For example,

- Although there is no scientific data to support this claim, many women have reported relief of symptoms when caffeine was reduced or eliminated from their diets. Decreasing salt before and during the period when breasts are most sensitive may also ease swelling and discomfort. Low-fat diets and elimination of dairy products also appear to decrease soreness for some women. However, it may take several months to realize the effects of these various treatments.
- Over-the-counter analgesics such as acetaminophen (Tylenol) or ibuprofen (Advil) may be recommended. In some cases, treatment with prescription drugs such as hormones or hormone blockers may prove successful. Oral contraceptives may also be prescribed.
- Warm soaks or ice packs may provide comfort. A well-fitted support bra can minimize physical movement and do much to relieve breast discomfort. Breast massage may promote removal of excess fluid from tissues and alleviate symptoms. Massaging the breast with castor oil, straight or infused with herbs or essential oils, can help reduce and dissipate fibroadenomas as well as keep women in touch with changes in their breast tissue.
- Infections are often treated with warm compresses and **antibiotics**. Lactating women are encouraged to con-

QUESTIONS TO ASK THE DOCTOR

- How common is this condition?
- Do cysts show up on mammography?
- Can fibrocystic condition of the breast lead to cancer?
- How can I tell the difference between cysts and cancer when I perform my breast self-exam?
- Can I do anything to prevent this condition?

tinue breastfeeding because it promotes drainage and healing. However, a serious infection may progress to form an abscess that may need surgical drainage.

- Some studies of alternative or complementary treatments, although controversial, have indicated that **vitamins** A, B complex and E, and mineral supplements may reduce the risk of developing fibrocystic condition of the breast. Evening primrose oil (*Oenothera biennis*), flaxseed oil, and fish oils have been reported to be effective in relieving cyclic breast pain for some women.

Prognosis

Most benign breast conditions carry no increased risk for the development of breast cancer. However, a small percentage of biopsies uncover overgrowth of tissue in a particular pattern in some women; this pattern indicates a 15–20% increased risk of breast cancer over the next 20 years. Strict attention to early detection measures, such as annual mammograms, is especially important for these women.

Prevention

There is no proven method of preventing the various manifestations of fibrocystic condition from occurring. Some alternative health care practitioners believe that eliminating foods high in methyl xanthines (primarily coffee and chocolate) can decrease or reverse fibrocystic breast changes.

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American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. 1-800-ACS-2345 <http://www.cancer.org>.

American College of Obstetricians and Gynecologists. 409 12th St., S.W., P.O. Box 96920, Washington, DC 20090-6920. <http://www.acog.org>.

Cancer Information Service (CIS). 9000 Rockville Pike, Building 31, Suite 10A18, Bethesda, MD 20892. Phone: 1-800-4-CANCER. Free telephone service provided by the National Cancer Institute.

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Fibrosarcoma

Definition

Fibrosarcoma is a malignant tumor that arises from fibroblasts (cells that produce connective tissue). This is a type of sarcoma that is predominantly found in the area around bones or in soft tissue.

Description

Fibrosarcomas are the result of fibroblasts, which produce connective tissue such as collagen. Fibrosarcoma tumors are consequently rich in collagen fibers. The immature, proliferating fibroblasts take on an interlacing, or herringbone, pattern.

Fibrosarcomas can form from fibroblasts in soft tissue such as muscles, connective tissues, blood vessels, joints, and fat. Soft tissue fibrosarcoma normally occurs in fibrous tissue of the body's trunk and the extremities such as the arms and legs. Soft tissue fibrosarcomas are extremely rare, with approximately 500 new cases reported each year.

Sarcomas of the bone

Fibrosarcoma can also occur in bones. While a bone is made up of inorganic molecules such as calcium phosphate, it also has an organic element made up of 95% collagen, similar to the collagen found in the skin. Fibrosarcomas of the bone usually occur in long bones in the bone marrow cavity where collagen is formed. The bones that predominantly yield fibrosarcomas are those in the legs, arms, pelvis, and hip.

Sarcomas of the bone are rare and represent about 0.2 percent of all new cancer cases each year. The two most common forms of bone cancer are **osteosarcoma** and **Ewing's sarcoma**. Among the less common are **chondrosarcoma**, fibrosarcoma, and **malignant fibrous histiocytoma**, all of which arise from spindle cell neoplasms.

Demographics

Fibrosarcomas typically develop in people between the ages of 25–79. The peak age of occurrence is 55–69 years. Generally, fibrosarcomas develop equally in men and women, though they are rare in children.

Infantile fibrosarcoma, also known as congenital fibrosarcoma or juvenile fibrosarcoma, is unique. Under microscopic examination, it is similar to fibrosarcomas seen in adults. However, infantile fibrosarcomas have a more positive prognosis with a post-treatment, five-year survival rate of 83% to 94%.

Causes and symptoms

Fibrosarcomas of the bone are sometimes connected with underlying benign bone tumors. Both fibrosarcomas of soft tissue and of the bone can develop as a result of exposure to radiation. This can result as a side effect from previous **radiation therapy** for unrelated primary cancer treatment. Individuals with other bone diseases, such as Paget's disease and osteomyelitis, are at a higher risk for developing fibrosarcomas.

There are many symptoms associated with the onset of fibrosarcomas. The following is a list of the main symptoms that may be present:

- pain
- swelling
- firm lump just under the skin or on a bone
- broken bone
- impeded normal range of motion
- neurologic symptoms
- gastrointestinal bleeding (seen in soft tissue abdominal fibrosarcomas)
- urinary frequency (seen in pelvic fibrosarcomas)
- urinary obstruction (seen in pelvic fibrosarcomas)

Diagnosis

In order to diagnose fibrosarcoma, a doctor will take the patient's medical history and will conduct a thorough physical exam. Blood tests will be performed to rule out other conditions and to identify cancer markers.

The most revealing initial exam is an **x ray**. It can show the location, size, and shape of the tumor. If a malignant tumor is present, the x ray will expose a soft tissue mass with ill-defined edges. This procedure takes less than an hour and can be performed in the doctor's office.

Once there is evidence of a tumor, one or more of several other procedures may be performed, including **computed tomography** (CT) scans, **magnetic resonance imaging** (MRI), angiograms, and biopsies.

Treatment team

The patient's primary care physician may perform the initial diagnostic tests. However, in order to comprehensively diagnose and treat fibrosarcomas, the primary care physician will refer the patient to an oncologist (cancer specialist). Radiologists, pathologists, and surgeons will also be involved to read x rays, examine tissue samples, and, if needed, remove the tumor.

Other individuals might be involved with the treatment of fibrosarcoma, including nurses, dieticians, and physical or vocational therapists.

Clinical staging, treatments, and prognosis

After the physician makes the diagnosis, it is important to determine the stage of the cancer. This will help reveal how far the cancer has progressed and how much tissue has been affected.

The American Joint Committee on Cancer developed the most widely used staging system for fibrosarcomas. The foremost categories of this system include grade (G), size of the tumor (T), lymph node involvement (N), and presence of metastases (M). Low grade and high grade are designated G1 and G3, respectively. The size of the tumor can be less than 5 centimeters (2 inches), designated as T1, or greater than 5 centimeters,

designated as T2. If the lymph nodes are involved, N1 is designated, while no lymph involvement is designated N0. Finally, there may be a presence of distant metastases (M1), or no metastases (M0). The following is a list of stages and their indications:

- Stage IA: (G1, T1, N0, M0)
- Stage IB: (G1, T2, N0, M0)
- Stage IIA: (G2, T1, N0, M0)
- Stage IIB: (G2, T2, N0, M0)
- Stage IIIA: (G3, T1, N0, M0)
- Stage IIIB: (G3, T2, N0, M0)
- Stage IVA: (Any G, any T, N1, M0)
- Stage IVB: (Any G, any T, N1, M1)

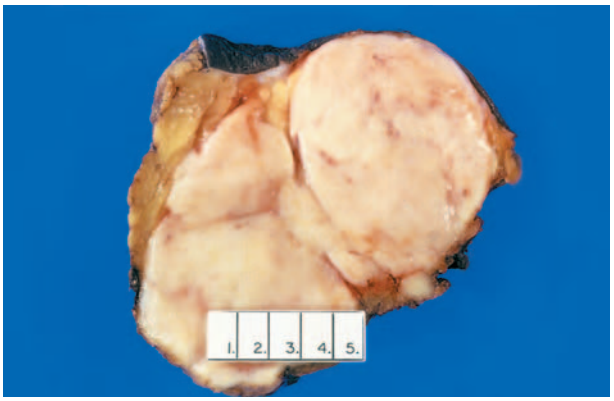
Tumors with lower stage numbers, such as IA and IB, contain cells that look very similar to normal cells, while tumors with higher stage designations are composed of cells that appear very different from normal cells. In higher staged tumors, the cells appear undifferentiated.

Physicians can employ several courses of treatment to remove fibrosarcomas. The most effective treatment is surgical removal; this is used as a primary treatment for all stages of fibrosarcoma. When performing the surgery, the surgeon will remove the tumor and some healthy soft tissue or bone around it to ensure that the tumor does not recur near the original site.

Prior to surgery, large tumors (greater than 5 centimeters, or 2 inches) may be treated with **chemotherapy** or radiation in order to shrink them, thus rendering the surgical procedure more effective.

Even individuals with low-grade fibrosarcoma who have undergone surgery experience a moderate risk of local recurrence. To combat recurrence, adjuvant chemotherapy (the use of one or more cancer-killing drugs) and radiation therapy (the use of high-energy rays), such as irradiation and brachytherapy, are also used to complement surgery. Employing chemotherapy or radiation therapy individually without surgery is much less effective.

After therapy, low-stage fibrosarcomas (stages IA and IB) have greater five-year survival rates than high stages (Stages IVA and IVB). Because high-grade tumors are more aggressive and more highly metastatic than lower grade tumors, patients with high-grade tumors have a lower survival rate. Not only is the grade of the tumor (the estimate of its aggressiveness) important in determining prognosis, the age of the patient is also crucial. Generally, fibrosarcomas that occur in childhood and infancy have a lower mortality rate than those that occur in adults. Additionally, patients with



Excised specimen of a skin tumor known as a fibrosarcoma, sliced open (white). *(Photo Researchers, Inc. Reproduced by permission.)*

fibrosarcomas that occur in the extremities have a better survival rate than those with fibrosarcomas in the visceral region.

Metastases appear later in the development of fibrosarcomas. The lungs are the primary sites of **metastasis** for fibrosarcomas that develop in the extremities. Once metastasis to the lungs has occurred, the chances of survival are significantly decreased.

Alternative and complementary therapies

Many individuals choose to supplement traditional therapy with complementary methods. Often, these methods improve the tolerance of side effects and symptoms, as well as enrich the quality of life. The American Cancer Society recommends that patients talk to their doctor to ensure that the methods they choose are safely supplementing their traditional therapy. Some complementary cancer therapies include the following:

- yoga
- meditation
- religious practices and prayer
- music therapy
- art therapy
- massage therapy
- aromatherapy

Coping with cancer treatment

Chemotherapy often results in several side effects, depending on the drug used and the patient's individual tolerance. Patients may have to deal with nausea, vomiting, loss of appetite (anorexia), and hair loss (**alopecia**).

KEY TERMS

Adjuvant—A treatment that has been added to a curative treatment to combat recurrence.

Brachytherapy—Radiotherapy that places the source of radiation close to the surface of the body or within a body cavity.

Carcinogen—An agent that is capable of causing cancer.

Epiphysis—The end of long tubular bones such as femur in the leg and the humerus in the arm.

Spindle cell—Cells shaped like a spindle, typically found in connective tissue.

Undifferentiated—Cells that have not matured normally and do not function properly.

Visceral—Having to do with an organ in the human torso.

Many times, chemotherapy as well as radiation therapy are better handled if patients are eating well. Nurses and dieticians can aid patients in choosing healthful foods to incorporate into their diet.

If the fibrosarcoma necessitated a limb **amputation**, then patients will need to learn how to cope with a prosthetic device. Both physical and vocational therapists can effectively help patients adjust and learn how to use the prosthetic device to perform their daily activities.

Clinical trials

Fibrosarcomas are rare, but advances are being made in both diagnostic and curative procedures. Although surgery is the most effective treatment, both pre- and post-operative adjuvant therapies are being researched to complement surgery.

Exploring the results of chemotherapy trials uncovers a trend of improved results with more intense regimens—meaning higher and more prolonged doses of drug therapy. Drugs that are being studied in 2001 include **cyclophosphamide**, **doxorubicin**, **methotrexate**, **vincristine**, **dacarbazine**, dactinomycin, or a combination of two or three of these.

Patients should consult with their physicians or contact the American Cancer Society to learn what procedures are currently being investigated in **clinical trials**. In some cases, insurance companies will not cover procedures that are part of clinical trials. Patients should talk with their doctor and insurance company to determine which procedures are covered.

QUESTIONS TO ASK THE DOCTOR

- What diagnostic procedures are best for the location and type of tumor suspected?
- What treatments are best for the location and type of tumor suspected?
- What kinds of side effects will this course of treatment cause?
- Are there support services available?
- What treatments are currently in clinical trials?
- What treatments will my health care insurance cover?
- What alternative treatments are safe?

Prevention

The prevention of cancer can be assisted by avoiding known chemical carcinogens such as alpha-naphthylamine, carbon tetrachloride, and benzene. Another way to avoid developing cancer is to minimize exposure to penetrating radiation such as x rays and radioactive elements. Medical x rays revolutionized the field of medicine and are used to detect and treat many diseases. In most cases, the benefits of medical x rays outweigh the risks.

Special concerns

Treatment, especially surgical amputation, can take a physical and psychological toll on cancer patients and their families. To deal with the psychological impact, there are many different support groups and psychotherapists that can help. Some therapists will consider amputation a posttraumatic stress disorder, and treat it accordingly. To deal with their condition, relying on faith practices can also be beneficial for cancer patients. Patients should discuss all options with their physician to determine what is available.

Once the cancer has been treated, patients should make sure to schedule follow-up appointments with their physicians. Physicians will want to monitor the patient for side effects or possible recurrence that may develop years after treatment.

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Filgrastim

Definition

Filgrastim is a medicine used to increase the white blood cell count in the body, which will help prevent infection. Filgrastim is known by the brand name Neupogen.

Purpose

Filgrastim is a drug approved by the Food and Drug Administration (FDA) to increase white blood cell counts. If a patient has a lower than normal white blood cell count it is referred to as **neutropenia**.

Filgrastim can be used to treat neutropenia caused by cancer **chemotherapy** treatment. In these patients the filgrastim increases the recovery of white blood cells after chemotherapy. Filgrastim can also be used to treat patients who have a neutropenia not related to chemotherapy. In both cases, the filgrastim decreases the risk of **fever** and infection.

Filgrastim is not usually used in leukemia patients. However, in patients with the disease known as acute myelocytic leukemia, it is approved for use after chemotherapy. Filgrastim can increase the recovery of the white blood cell count thereby decreasing the length of time a patient may have a fever associated with a low white count.

Filgrastim can also be used after bone marrow transplantation. Once the new healthy bone marrow has been given back to a patient, filgrastim can be administered to help increase the white blood cell count and decrease the risk of fever and infection.

Filgrastim can be used for patients who will receive a peripheral blood stem cell transplant. Patients will receive the filgrastim before the transplant. The filgrastim in these patients causes young, non-developed blood cells, known as stem or progenitor cells, to move from the bone marrow to the blood where they will then be removed from a patient by the process of apheresis. These blood cells are stored until after the patient receives larges doses of chemotherapy that destroy the bone marrow and the cancer. The patient then receives these stored cells back by an intravenous infusion. The stored cells repopulate the bone marrow and develop into the many types of functioning blood cells.

Description

Filgrastim has been available to cancer patients since the 1990s, and is highly effective at decreasing neutropenia. Filgrastim may be referred to as G-CSF, granulocyte colony stimulating factor, colony stimulating factor. This compound is manufactured by recombinant DNA methods using E. coli as the host organism. Chemotherapy destroys white blood cells temporarily. These white blood cells will grow again, but during the time that the levels are low, patients are at an increased risk of developing fevers and infection. Filgrastim acts to stimulate the bone marrow to make more white blood cells, which can either prevent the white count from dropping below normal or decrease the time that the level is low. By effectively avoiding fevers and infections, patients are able to receive their next doses of chemotherapy without delay.

Recommended dosage

Filgrastim is a clear colorless liquid that is dosed on body weight in kilograms. It is kept refrigerated until ready to use, and it is administered to patients as a subcutaneous injection (directly underneath the skin) It is usually administered in the back of the arms, upper legs, or stomach area. Filgrastim can also be given to patients as a short intravenous infusion into a vein over 15 to 30 minutes.

Chemotherapy-caused neutropenia

The starting dose for patients who have just finished chemotherapy is 5 micrograms per kilogram of body weight per day. This is given as a subcutaneous injection under the skin daily for up to 14 consecutive days, and sometimes longer. The doctor will inform the patient when it is time to stop the filgrastim.

Bone marrow transplants

The recommended dose is 10 micrograms per kilogram per day. This can be administered as a 4- to 24-hour infusion intravenously, or as a 24-hour subcutaneous infusion.

Peripheral blood stem cell transplant

The recommended dose is 10 micrograms per kilogram per day. This can be given either as a under the skin injection, intravenously, or as a continuous infusion over 24 hours. This dosing should begin four days before the first apheresis collection process and continue until the last day of collection.

Other neutropenia

The dose recommendation is variable based on the reason for neutropenia. The range of filgrastim doses has been from 5 micrograms per kilogram per day up to 100 microgram per kilogram per day. Doctors may increase the filgrastim dose based on how the white blood cell count responds to the treatment. Other factors that play a role in filgrastim dosing include how low the white blood cell count is and the length of time the white blood cell count remains low.

Precautions

Filgrastim should not be received by a patient in the 24-hour time frame before or after receiving chemotherapy or reinfusion of bone marrow or stem cells.

Blood counts will be monitored while on the drug filgrastim. This allows the doctor to determine if the drug is working and when to stop the drug.

It is not recommended to give filgrastim to patients who have certain types of leukemias.

Patients with a known previous allergic reaction to filgrastim or to any other substance derived from the bacteria *E. coli* should not take filgrastim.

Patients who may be pregnant, or trying to become pregnant, should tell their doctor before receiving filgrastim.

Side effects

The most common side effect from filgrastim is **bone pain**. The filgrastim causes the bone marrow to produce more white blood cells, and, as a result, patients may experience pain in their bones. Tylenol, an over-the-counter pain reliever, can usually control mild to moderate pain that occurs with standard dosed filgrastim. Larger doses of filgrastim, like those given for bone marrow transplant patients, can cause severe bone pain that may need a prescription pain reliever to ease the pain.

Another common side effect due to filgrastim administration is pain or burning at the site of the injection. This can be decreased by bringing the filgrastim to room temperature before administering the injection, icing the area of injection to numb it before receiving the injection, and moving the site of the injection with each dose.

Patients who have received filgrastim after cancer chemotherapy have reported fever, nausea and vomiting, muscle pain, **diarrhea**, hair loss (alopecia), mouth sores, fatigue, shortness of breath, weakness, headache, cough, rash, constipation, and pain. These side effects may be due to the chemotherapy administration.

KEY TERMS

Food and Drug Administration (FDA)—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives the approval to pharmaceutical companies for commercial marketing of their products.

Chemotherapy—Specific drugs used to treat cancer.

Subcutaneous—Underneath the initial layer of skin.

Intravenous—To enter the body through a vein.

Reinfusion—The transfer through a vein of healthy stem cells or bone marrow to a patient that had received larges doses of chemotherapy used to destroy cancer cells.

Neutropenia—Low white blood cell count.

Recovery—Blood counts that are returning back to normal levels.

Apheresis—The process of removing and collecting specific cells from the blood through a machine.

Peripheral blood stem cell transplant—A procedure that collects and stores healthy young and non-developed blood stem cells. These are then given back to a patient to help them recovery from high doses of chemotherapy that they received to destroy their cancer.

Bone marrow transplant—A procedure that destroys all of a patients' diseased bone marrow and replaces it with healthy bone marrow.

Interactions

Filgrastim should not be given at the same time as chemotherapy or **radiation therapy**. Dosing should begin at least 24 hours after the last dose of treatment.

Patients on the drug lithium should tell their doctor before starting filgrastim therapy.

Filgrastim use for delayed **myelosuppression** has not been studied after the use of the chemotherapy agents **mitomycin-C**, and nitrosoureas, or after the drug **fluorouracil**.

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Flow cytometry

Definition

Flow cytometry, is a method of sorting and measuring types of cells by fluorescent labeling of markers on the surface of the cells. It is sometimes referred to as FACS (Fluorescent Activated Cell Sorting) analysis.

Purpose

Flow cytometric analysis is most often clinically used to help determine the type of leukemia or **lymphoma** a patient has and to assess the prognosis. Flow cytometry is quite sensitive; it is able to detect rare cell types and residual levels of disease.

Precautions

Drugs, such as steroids, that suppress the immune system will affect the number of white blood cells in the patient's sample.

Description

The physician will select a sample based on the type of cancer the patient is thought to have. In the case of lymphoma, the sample may be collected by fine needle aspiration **biopsy**, then the tissue sample will be separated into single cells. Analysis of leukemia will require a patient to give a blood sample. The patient's blood sample will be separated and the red blood cells removed. The sample will be mixed with a variety of different antibodies that can interact with markers on the surface of the cells. Different types of cells have characteristic markers on their cell surfaces, so a particular cell type can be identified by the antibodies that bind to it. The antibodies are labeled so that they will give off fluorescent light (glow) as they pass through the laser beam in the cytometer. The cytometer also measures the size of the cell and some information about the interior of the cell. The physician uses this information to determine the specific type of leukemia, such as myelogenous or lymphocytic, which in turn, helps to determine the type of treatment that will be best suited to the patient.

Sample analysis may also be performed using a more complex type of flow cytometer combined with a microscope, called a laser-scanning cytometer. This instrument is similar to a regular flow cytometer, but is better able to analyze solid tumor samples.

Preparation

Flow cytometry is usually performed on blood, body fluids, or bone marrow. In most cases, no special preparation is required. If bone marrow aspiration is necessary or a biopsy is required from a solid tumor, the patient should be appropriately prepared for these procedures. However, the flow cytometry itself does not require any additional preparation on the part of the patient.

KEY TERMS

Antibody—A protein formed by the immune system (white blood cells) which reacts with a specific antigen.

Cytometer—An instrument that measures cells.

Fluorescence—Light absorbed at one wavelength and emitted at another. That is, it glows.

Aftercare and Risks

The only aftercare and risks associated with flow cytometric analysis are those associated with the sample collection procedure. The cell analysis itself requires no effort or risk from the patient.

Normal results

A normal result will indicate that there is no increase in the number of any particular type of immune cell. The pathologist will see several different types of cells, but no one type will be present in increased numbers.

Abnormal results

If the results are abnormal, the pathologist will observe an unusually large number of one particular cell type. The types of marker present on the cell will give further information about the type of leukemia or lymphoma and may indicate the patient's prognosis. For example, leukemic cells that have markers that are normally found on less mature cell types may suggest a poorer prognosis, and therefore more aggressive therapy may be recommended.

See also Tumor grading.

Resources

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QUESTIONS TO ASK THE DOCTOR

- What type of information do you expect to learn from this test?
- Are there any alternatives to doing this test?
- Are there any risks or complications?
- Are there any special preparations required?
- Is it possible that the test may give unclear or inaccurate results?
- Is this the best way to tell if, or what type of cancer I have?

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Floxuridine

Definition

Floxuridine is an anti-cancer drug that is injected directly into the artery that carries blood to the liver or the abdominal cavity. The brand names of floxuridine are Fluorodeoxyuridine, FUDR, and Floxuridine For Injection USP. The generic name product may be available in the United States.

Purpose

Floxuridine is used to treat **gastrointestinal cancers** that have metastasized, or spread, to the liver. These cancers include **rectal cancer** and Stage IV **colon cancer**. Floxuridine also has been used to treat cancerous gastrointestinal tumors; however the response rate is poor and usually the drug is used only to relieve symptoms.

Description

Floxuridine is approved by the United States Food and Drug Administration.

Floxuridine is a type of medicine called an antimetabolite because it interferes with the metabolism and growth of cells. Floxuridine prevents the production of DNA in cells. The cells cannot reproduce and eventually they die.

Floxuridine sometimes is used in conjunction with the drugs **fluorouracil** (5-FU), **cisplatin**, and/or **leucovorin**. Leucovorin increases the activity of floxuridine. In general, floxuridine is more effective than other chemotherapies against liver metastases, but its use does not improve overall survival rates. Ongoing studies are comparing floxuridine with other chemotherapies. The drug may be used in conjunction with surgery. Its use in conjunction with **radiation therapy** is being evaluated.

Recommended dosage

Floxuridine is injected directly into the liver. This is called hepatic intra-arterial infusion, or **hepatic arterial infusion**. A special pump delivers the drug through an implanted infusion port or catheter into an artery that goes to the liver. Injection of floxuridine into a vein is being evaluated. Floxuridine also may be injected into the abdominal cavity (intraperitoneal therapy). The dosage of floxuridine depends on a number of factors including body weight, type of cancer, and any other medicines that are being used.

Precautions

Floxuridine may lower the number of white blood cells and, therefore, reduce the body's ability to fight infection. Immunizations (vaccinations) should be avoided during or after treatment with floxuridine because of the risk of infection. It also is important to avoid contact with individuals who have recently taken an oral polio vaccine. Treatment with floxuridine may cause chicken pox or shingles (**Herpes zoster**) to become very severe and spread to other parts of the body.

Kidney or liver diseases may increase the effects of floxuridine, since the drug may be removed from the body at a slower rate. Floxuridine also may put an individual at an increased risk for hepatitis.

Floxuridine can cause birth defects in animals. Therefore this drug should not be taken by pregnant women or by either the man or the woman at the time of conception. Women usually are advised against breastfeeding while receiving this drug.

Side effects

Since floxuridine may affect the growth of normal cells as well as cancer cells, side effects may occur during or after drug treatment. Some effects may occur months or even years after the drug is administered.

Floxuridine increases the risk of later developing certain types of cancer, such as leukemia.

The more common side effects of floxuridine include:

- diarrhea
- loss of appetite (anorexia)
- sores in the mouth or on the lips
- stomach pain or cramps
- numbness or tingling in the hands and feet

Less common side effects of floxuridine include:

- nausea and vomiting
- black, tar-like stools
- heartburn
- redness or scaling of the hands or feet
- sore, swollen tongue
- skin rash or itching
- temporary thinning of hair (alopecia)
- bleeding at the site of the catheter
- infection from the catheter
- closing off of the catheter

Other, rare side effects of floxuridine include:

- blood in urine or stools
- hiccups
- hoarseness or coughing
- fever or chills
- sore throat
- difficulty swallowing
- blurred vision
- lower back or side pain
- painful or difficult urination
- small red skin spots
- difficulty walking
- bleeding or bruising
- yellow eyes or skin
- seizures
- depression

In addition to lowering the white blood cell count, increasing the risk of infection, floxuridine may reduce the level of blood platelets that are necessary for normal blood clotting. This can increase the risk of bleeding. The drug also may lead to abnormalities in liver function. Intraperitoneal floxuridine therapy has been associated with the development of fibrous masses in the abdomen.

KEY TERMS

Catheter—Tube used to inject medicine into the body.

Hepatic intra-arterial infusion—Injection of medicine into the artery to the liver.

Intraperitoneal—Within the abdominal cavity.

Metastasis—Spread of cancer from its point of origin to other parts of the body.

Interactions

Previous treatment with radiation or other anti-cancer drugs can increase the effects of floxuridine on the blood.

Drugs that may interact with floxuridine include:

- amphotericin B (Fungizone)
- antithyroid drugs that are used to treat an overactive thyroid
- azathioprine (Imuran)
- chloramphenicol (Chloromycetin)
- colchicine
- flucytosine (Ancobon)
- ganciclovir (Cytovene)
- interferon (Intron A, Roferon-A)
- plicamycin (Mithracin)
- zidovudine (AZT, Retrovir)

Margaret Alic, Ph.D.

Fluconazole *see* **Antifungal therapy**

Fludarabine

Definition

Fludarabine is a **chemotherapy** medicine used to treat certain types of cancer by destroying cancerous cells. It is known as the brand name Fludara. Fludarabine may also be referred to as Fludarabine phosphate, 2-fluoroadenine aribinoside 5-phosphate, and FAMP.

Purpose

Fludarabine is approved by the Food and Drug Administration (FDA) to treat refractory **chronic lymphocytic leukemia** (CLL). Patients must have a disease that did not respond to other treatment or a disease that became worse during other treatment. Fludarabine has also been used to treat Hodgkin's and non-Hodgkin's **lymphoma**, **cutaneous T-cell lymphoma**, macroglobulinemic lymphoma, **mycosis fungoides**, and **hairy cell leukemia**.

Description

Fludarabine has been available for use since the early 1990s, and is a member of the group of chemotherapy drugs known as antimetabolites. Antimetabolites interfere with the genetic material (DNA) inside the cancer cells and prevent them from further dividing and growing more cancer cells.

Recommended dosage

Fludarabine is a clear solution that is administered through a vein.

A fludarabine dose can be determined using a mathematical calculation that measures a person's body surface area (BSA). This number is dependent upon a patient's height and weight. The larger the person, the greater the body surface area. BSA is measured in the units known as square meter (m^2). The body surface area is calculated and then multiplied by the drug dosage in milligrams per square meter (mg/m^2). This calculates the actual dose a patient is to receive.

The approved dose for chronic lymphocytic leukemia is 25 milligrams per square meter per day for 5 days in a row. The fludarabine is given intravenously into a vein over a 30-minute to 2-hour time period. This 5-day cycle is repeated every 4 weeks.

The dose of fludarabine may need to be decreased in patients who have kidney problems.

Precautions

Blood counts will be monitored regularly while on fludarabine therapy. During a certain time period after receiving fludarabine, there is an increased risk of getting infections. Caution should be taken to avoid unnecessary exposure to crowds and people with infections.

Patients with a known previous allergic reaction to chemotherapy drugs should tell their doctor.

Patients who may be pregnant or are trying to become pregnant should tell their doctor before receiving fludarabine. Chemotherapy can cause men and women to be sterile, or unable to have children. It is unknown if fludarabine has this effect on humans.

Patients should check with their doctors before receiving live virus **vaccines** while on chemotherapy.

KEY TERMS

Anemia—A red blood cell count that is lower than normal.

Chemotherapy—Specific drugs used to treat cancer.

Deoxynucleic acid (DNA)—Genetic material inside of cells that carries the information to make proteins that are necessary to run the cells and keep the body functioning smoothly.

Electrolytes—Elements normally found in the body (sodium, potassium, calcium, magnesium, phosphorus, chloride, and acetate) that are important to maintain the many cellular functions and growth.

Food and Drug Administration (FDA)—The government agency that oversees public safety in relation to drugs and medical devices, and gives the approval to pharmaceutical companies for commercial marketing of their products.

Gout—A disease caused by the build up of uric acid in the joints causing swelling and pain.

Intravenous—To enter the body through a vein.

Neutropenia—A white blood cell count that is lower than normal.

Refractory—Cancer that no longer responds to treatment.

Side effects

The most common side effect expected from taking fludarabine is low blood counts (**myelosuppression**). When the white blood cell count is lower than normal (**neutropenia**), patients are at an increased risk of developing a **fever** and infections. Patients may need to be treated with **antibiotics** at this point. The platelet blood count can also be decreased due to fludarabine administration, but generally returns to normal within 2 weeks after the end of the infusion. Platelets are blood cells that cause clots to form to stop bleeding. When the platelet count is low, patients are at an increased risk for bruising and bleeding. Fludarabine causes low red blood cell counts (**anemia**). Low red counts make people feel tired and dizzy.

Fludarabine can cause the development of autoimmune **hemolytic anemia**, which occurs when the body begins to destroy its own red blood cells. It is an uncommon side effect, but very serious when it occurs.

Common side effects from fludarabine include **nausea and vomiting**. If nausea and vomiting are a problem, patients can be given **antiemetics** before receiving fludarabine. This medication helps prevent or decrease these side effects. Other common side effects include fever, chills, joint pain, fluid gain, fatigue, sleepiness, pain, muscle ache, weakness, and infection. Other less common side effects include loss of appetite (anorexia), **diarrhea**, abnormal touch sensation, cough, **pneumonia**, and shortness of breath.

Damage to the nerves and nervous system tissues can occur with fludarabine. Side effects due to this nerve damage include sleepiness, confusion, weakness, fatigue, irritability, numbness or tingling in the hands and feet, visual changes, and difficulty walking.

Infrequent side effects of fludarabine are skin rashes, pain, **itching**, fever, lung problems, insomnia, headache, muscle and joint aches, swelling, and decreased blood pressure.

Rare side effects of fludarabine include mouth sores, constipation and abdominal cramping, bleeding from the bladder, hair loss, hearing problems, and liver and kidney problems.

Fludarabine can cause the rapid breakdown of cancer cells. Patients who have large numbers of cancer cells in their bloodstream can develop a problem known as **tumor lysis syndrome**. The symptoms of this syndrome include pain in the lower back and blood in the urine. A patient can develop high or low levels of electrolytes and high levels of uric acid, which can lead to gout and kidney damage. The drug **allopurinol** may be given to patients prior to fludarabine treatment to prevent this from occurring. Drinking an increased amount of liquids also may help prevent the kidney damage.

All side effects a patient experiences should be reported to the doctor.

Interactions

Fludarabine should not be used in combination with the drug **pentostatin**. The combination causes severe lung damage.

Nancy J. Beaulieu, R.Ph., B.C.O.P.

Fluorouracil

Definition

Fluorouracil is a medication that kills cancer cells. It is also known as 5-FU or 5-fluourouracil, and as the brand name Adrucil.

Purpose

5-FU may be used in combination with other **chemotherapy** agents to treat cancers of the breast, stomach, colon, rectum, and pancreas.

Description

5-FU is a cytotoxic drug. This means that it kills cancer cells. 5-FU kills cells by interfering with the activities of DNA and RNA, which are molecules in the cells important in expressing genetic material.

Recommended dosage

Most frequently, 5-FU is given as an injection into the vein (intravaneous injection or IV). Many different doses and regimens are used depending on the cancer diagnosis, and patients should discuss with their physician the dose based on the individual protocol used. A sample dose is 500 to 1,000 mg per square meter of body surface area given as a 24-hour infusion for four to five days every three weeks. A dose of 425 mg per square meter of body surface area per day for five days given along with the drug **leucovorin** is also common.

Precautions

Patients with allergic reaction to 5-FU should not be administered this drug. It is also inadvisable for pregnant women. 5-FU should be administered with caution to patients with impaired liver or kidney function, or in patients with a history of heart problems.

Side effects

The amount of drug given and the duration of which it is given during a single session greatly influences the side effects seen. For example, when given as a 24-hour continuous infusion, the most common side effects are **diarrhea** and mouth ulcers. If 5-FU is given as a bolus infusion (a high quantity of the drug all at once), the most common side effect is bone marrow suppression; this results in a decrease of the white blood cells responsible for fighting infections, the platelets responsible for blood clotting, and the red blood cells responsible for providing oxygen to the cells of the body.

The severity of the side effects is increased when 5-FU is given with the drug leucovorin. Vomiting, diarrhea, nausea, and loss of appetite (anorexia) may occur regardless of how 5-FU is administered. The diarrhea side effect may be severe in some patients, and it is important for them to alert their doctor immediately so that appropriate medications for the diarrhea can be prescribed.

5-FU may cause rashes, increased sensitivity to sunlight, changes in skin color, changes to the fingernails, and

KEY TERMS

Cytotoxic drug—A medicine that kills (cancer) cells.

DNA—A molecule found in all living cells that contains tiny bits of genetic information.

Infusion therapy—Administration of a medication as a liquid through an intravenous (IV) device.

RNA—A molecule found in all living cells that plays a role in transmitting information from the DNA to the protein-forming system of the cell.

redness and swelling in the palms of the hands and soles of the feet. Patients who have had heart disease before starting therapy with 5-FU may have problems with blood flow to the heart. Rarely, 5-FU may cause an allergic reaction, dry eyes, sleepiness, confusion, headache, changes in walking gait, involuntary rapid movement of the eyes, and difficulty speaking. When 5-FU is applied directly on the skin, there are usually no side effects except for those to the skin itself. These may include burning sensations, pain, and darkening of the skin color.

Some authorities recommend discontinuation of 5-FU therapy as soon as mild side effects are observed as a way of reducing the extent of injury to the digestive tract. Administration may then be restarted at a lower dose after the side effects have stopped.

Interactions

People taking fluorouracil should consult their doctor before taking any other prescription drug, over-the-counter drug, or herbal remedy.

Bob Kirsch

Fluoxymesterone

Definition

Fluoxymesterone is a synthetic male hormone used to treat women with hormone-dependent **breast cancer**, and may also be used as a **testosterone** replacement for men. Fluoxymesterone is sold as Halotestin, Android-F, and Ora-Testryl.

Purpose

Fluoxymesterone is used to manage metastatic breast cancer in menopausal women who have hormone receptor–positive tumors. It may also be used as a supplement to **chemotherapy** for metastatic breast cancer, or as a hormone replacement for men. Additionally, it is sometimes used to treat **anemia**.

Description

Fluoxymesterone is a synthetic androgen, or male hormone, similar in action to testosterone. Fluoxymesterone works by attaching itself to androgen receptors; this causes it to interact with the parts of the cell involved in the making of proteins. It may cause an increase in the synthesis of some proteins or a decrease in the synthesis of others. These proteins have a variety of effects, including blocking the growth of some types of breast cancer cells, stimulating cells that cause male sexual characteristics, and stimulating the production of red blood cells.

When used as a breast cancer treatment, this drug blocks the growth of tumor cells that are dependent on female hormones to grow. It can only be used on female breast cancer patients who have reached menopause one to five years earlier, or as a result of surgery. It may be used in addition to other chemotherapeutic drugs, such as **tamoxifen** or **cyclophosphamide**, **doxorubicin**, and **fluorouracil**.

Fluoxymesterone may be used to treat men; it replaces male hormones which are not being released in the body as a result of tumors, radiation, or surgery affecting the pituitary or hypothalamus.

Recommended dosage

The recommended dosage will depend on the age, sex, and diagnosis of the patient, as well as the response to treatment and occurrence of side effects. Treatment is usually with a full therapeutic dose initially, then adjusted to the individual needs of the patient.

Women being treated for breast cancer usually take 10 to 40 mg per day orally, divided into several doses. Up to three months may be required for a response to treatment.

Androgen replacement therapy for men is usually started at 5 to 20 mg per day, taken orally in divided doses.

If a dose is missed, it should be taken as soon as it is remembered, unless it is more than two hours late. If it is more than two hours late, the patient should skip that dose and continue to follow the normal dosing schedule.

Precautions

Fluoxymesterone may be taken with food if it causes stomach upset. Patients taking this medication should

ensure that they see their physician regularly during treatment and receive appropriate laboratory tests. Liver function should be monitored and cholesterol and red blood cell levels may need to be examined during treatment. Female breast cancer patients should have their serum and urine calcium levels checked. Prepubescent males will require x rays to determine the rate of their bone maturation. Diabetics should be aware that this medication may affect blood sugar levels.

Fluoxymesterone should not be taken by pregnant women as it will affect the sexual development of the fetus. The hormone may also pass into the milk of nursing mothers, affecting sexual development of the infant. Fluoxymesterone should not be taken by people with liver, kidney, heart or blood vessel disease, prostate problems, or sensitivity to the dye tartrazine. Patients with migraines or epilepsy should discuss these conditions with their physician before using the drug. Elderly male patients using fluoxymesterone have an increased risk of prostate enlargement.

Patients should consult their physician before discontinuing the drug.

Side effects

Patients who use fluoxymesterone have an increased risk of developing liver disease, and should report symptoms such as yellowing of the eyes and skin to their physicians immediately. Women being treated for breast cancer and patients who are immobilized may develop **hypercalcemia**. Other side effects which may occur include the following:

- fluid retention
- nausea and vomiting
- diarrhea
- anxiety
- depression
- changes in sex drive
- dizziness
- suppression of blood clotting factors II, V, VII, and X
- headache
- itching
- reduction in number of white blood cells
- increase in number of red blood cells

Women who take this medication may also experience menstrual irregularities, acne, enlarged clitoris, and masculine characteristics such as deepening of the voice, increased hair growth, and male pattern baldness. Some of these changes may go away if the medication is stopped, while others may remain.

KEY TERMS

Androgen—a male hormone

Hypercalcemia—high levels of calcium in the blood

Men taking fluoxymesterone may experience breast growth, erections of excessive frequency and duration, impotence, decreased ejaculatory volume, and bladder irritation.

Interactions

A large number of medications may cause interactions with fluoxymesterone, including acetaminophen, anabolic steroids, anticoagulants, antidiabetic agents, and many others. Patients should notify their physicians of any medications they are taking before using fluoxymesterone.

Racquel Baert, M.Sc.

Flutamide *see* **Antiandrogens**

Folic acid

Definition

Folic acid is a water-soluble B vitamin essential in the human diet. It is an important cofactor in the synthesis of DNA and RNA of dividing cells, particularly during pregnancy and infancy when there is an increase in cell division and growth.

Purpose

Folic acid is important to the field of oncology in two ways. First, prior to neoplasm formation, folic acid is important in the synthesis of DNA and RNA and the repair of damaged DNA. Second, after a tumor develops, a form of folic acid is used to counter the side effects of **methotrexate** and 5-fluorouracil (also called fluorouracil or 5-FU).

Description

Prior to tumor formation

Since folic acid is a cofactor in DNA replication and biosynthesis of purines and also in DNA repair, there is an increasing amount of research (epidemiological, clinical, and experimental) that suggests a folic acid deficiency might be a factor that predisposes the formation

of tumors in normal epithelial tissue. There is an inverse relationship associated with low folate diets and an increase in DNA breakage and mutation that is unable to be effectively repaired. The preventative influence of dietary folic acid on the formation of **colon cancer** is currently under heavy research. Although a correlation is observed, it has not yet been proven to show cause and effect. However, there is enough evidence to encourage consuming minimal daily dietary requirements of folic acid to potentially reduce the risk. When choosing supplements, other names for folic acid that may be encountered are folate and folacin.

After tumors form

Once a neoplasm forms, folic acid levels need to be decreased. In neoplasms, DNA replication and cell division are both occurring in an uncontrolled manner. Folate, which assists in this process, needs to be inhibited, causing an interruption in DNA synthesis and slowing the growth of the tumor. Chemotherapeutic agents called antimetabolites, or folic acid antagonists, such as methotrexate and 5-fluorouracil (5-FU), inhibit the enzymatic pathways for biosynthesis of nucleic acids by substituting for folic acid and sabotaging the reaction. Unfortunately, drugs that inhibit the biosynthesis of cancer cells also inhibit the biosynthesis of normal cells, resulting in extremely toxic side effects. To counter the side effects, a drug called **leucovorin** (a form of folate also known as Wellcovorin, Citrovorum and folinic acid) opposes the toxic effects of methotrexate on normal tissue. Leucovorin also increases the anticancer effect of 5-FU.

Recommended dosage

Non-cancer individuals supplementing their diet with folic acid may reduce the risk of cancer. Supplemental folic acid can be purchased over the counter and is also fortified in breakfast cereals and whole grain products produced in the United States. The recommended intake for adults is 400 micrograms (mcg) each day. While the risk of upper limit toxicity is low, adult men and women should not exceed the advised upper limit of 1,000 mcg per day. It is especially important that individuals diagnosed with cancer seek the advice of medical professionals before commencing or continuing supplemental folic acid use because it may interact with **chemotherapy**.

Cancer patients treated with methotrexate may be given leucovorin as a "rescue" treatment approximately 24 hours later to counteract the toxic side effects on normal tissues of the gastrointestinal system and bone marrow. Leucovorin is only available by prescription. It is a systemic drug available in oral form (tablets) or via injections. The dosage varies from person to person and is based on body size.

KEY TERMS

Folic acid antagonist—a drug that interferes with the action of folic acid

Neoplasm—abnormal tissue growth that is not controlled by normal stimuli and lacks normal structural organization

Purines—a substance that is part of the structure of guanine and adenine, molecules that combine to form DNA

Precautions

Patients should inform their physician of the following conditions before they begin to take leucovorin:

- Pregnancy or breast-feeding.
- Pernicious anemia.
- Allergies to leucovorin or any other drugs.
- Vitamin B_{12} deficiency. Folic acid may mask hematologic signs of B_{12} deficiency while neurologic damage progresses.

Side effects

Folic acid in general and specifically leucovorin are usually well-tolerated. However, there are some uncommon side effects that include skin rashes, **itching**, vomiting, nausea, **diarrhea**, and difficulty breathing. Although extremely rare, seizures have occurred in some patients taking leucovorin. Since leucovorin is taken with chemotherapeutic drugs, some side effects may be due to drug interaction.

Interactions

Supplemental folic acid can interact with anti-convulsant medications such as dilantin, **phenytoin**, and primidone. It also complicates the effects of metformin (used in individuals with type 2 diabetes), sulfasalazine (used in individuals with Crohn's disease), and triamterene (a diuretic).

Leucovorin enhances the effects of 5-FU and antagonizes the effects of methotrexate. It additionally interacts with barbiturate medications that may be taken by people with sleep disorders.

Sally C. McFarlane-Parrott

Foscarnet *see* **Antiviral therapy**

G

Gabapentin

Definition

Gabapentin is indicated to be used in combination with other anti-seizure (anticonvulsant) drugs for the management of partial seizure types. Gabapentin should not be used alone for the treatment of seizures unless the patient cannot tolerate other anticonvulsant drugs. This medication can also be used for the treatment of certain syndromes associated with nerve (neuropathic) pain (diabetic **neuropathy**, postherpetic neuralgia), pain associated with multiple sclerosis, neuropathic cancer pain, trigeminal neuralgia, and bipolar mood disorder. Gabapentin is also known as Neurontin.

Description

Gabapentin was introduced in 1994 as an anticonvulsant medication. Other medications in the anticonvulsant class include **phenytoin**, **carbamazepine**, phenobarbital, valproic acid, topiramate, and lamotrigine. Gabapentin's structure is similar to that of gamma-aminobutiric acid (GABA), which is a chemical found in the central nervous system (brain and spinal cord) that decreases firing of neurons leading to a decrease in seizure activity. Despite this structural similarity, gabapentin does not interact with GABA receptors and its exact mechanism of action for either epilepsy or pain is not known.

Gabapentin is a relatively recent addition to the arsenal of drugs used in the treatment of neuropathic pain. Traditionally, tricyclic antidepressants (**amitriptyline**, nortriptyline, desipramine) have been used as first-line agents. It takes one to three weeks for either gabapentin or tricyclic antidepressants (TCAs) to provide relief of pain after starting treatment. Gabapentin appears to be a safer agent to use than TCAs, especially in elderly patients and patients on multiple other medications. One of the disadvantages of gabapentin over TCAs is its higher cost.

Recommended dosage

Adults and children over 12 years of age

MANAGEMENT OF PARTIAL SEIZURE TYPES Therapy should be started at a dose of 300 mg, three times daily. The dose can be increased to 1,800 mg/day in three divided doses. Some patients may need even higher doses to control their seizures. Doses up to 3,600 mg per day have been well tolerated in research studies.

TREATMENT OF NEUROPATHIC PAIN Dosages of 300-3,600 mg/day have been effective in research studies. However, optimal dosage appears to be 1,200-2,400 mg/day divided in three doses.

TREATMENT OF BIPOLAR DISORDER Optimal dose has not been well established. Doses up to 4,800 mg/day have been used.

Children less than 12 years of age

Dosage varies due to the child's size, weight, and extent of condition. Parents should ask their physician about appropriate dosage levels for their child.

Administration

To minimize side effects, the first dose should be taken at bedtime. Capsules should not be chewed or crushed. Patients should avoid taking antacids (Mylanta, Maalox) at the same time as gabapentin. Doses should be taken at even intervals, and if a dose is missed, it should be taken as soon as remembered. However, double-doses can be hazardous and should be avoided.

Precautions

Gabapentin should be used with caution by breast-feeding mothers, children under 12 years of age (because of a lack of safety and efficacy studies in this population), and patients with impaired kidney function.

Gabapentin has resulted in fetal abnormalities in mice, rats, and rabbit offsprings. There are no current

KEY TERMS

Bipolar disorder—Recurrent mood disorder equally common among men and women, in which patients have extreme mood alterations between depression and mania or a mix of both. During manic episodes patients may have elevated mood, decreased need for sleep, rapid speech, extreme involvement in pleasurable activities, and may be easily distracted. The drugs commonly used in treatment of bipolar disorder include lithium, carbamazepine, valproic acid, and antidepressants.

Diabetic neuropathy—A chronic complication of diabetes that can take two forms, peripheral and autonomic. Patients with peripheral neuropathy experience dullness of sensation of pain, temperature, and pressure, especially in lower legs and feet. Autonomic neuropathy can cause alteration in bowel habits, impotence, and decreased heart function. The peripheral type can be treated with medications such as amitriptyline or gabapentin, while the autonomic type is more resistant to treatment.

Multiple sclerosis—A disorder of central nervous system, causing patches of plaques in brain and spinal cord and usually affecting young adults. Patients may experience visual changes, weakness, numbing or tingling of the hands or feet, changes in bladder and mood patterns.

Postherpetic neuralgia—Severe stabbing or throbbing pain associated with herpes zoster infection (shingles), resulting from the inflammation of nerve endings where the herpes vesicles erupt.

Trigeminal neuralgia—Severe, sudden bursts of throbbing and stabbing pain in one of the branches of trigeminal nerve located on the face. The pain can affect any area of the face, teeth, or tongue, and is often caused by some trigger points around the mouth.

studies on gabapentin use in pregnant women. This drug should only be used during pregnancy if potential benefits justify the risk to the baby.

This medication should not be discontinued suddenly because of the possibility of increased frequency of seizures. Gabapentin doses should be decreased gradually over a period of at least one week.

Gabapentin may cause drowsiness and dizziness. Alcoholic beverages may intensify these effects and their intake should be limited. Patients should use caution when driving, operating dangerous machinery, or performing activities requiring alertness.

A patient experiencing any of the following should contact their physician or pharmacist immediately:

- mental or mood changes
- tingling or numbness of hands or feet
- swelling of ankles
- vision problems
- fever or unusual bleeding

Side effects

This medication is usually well tolerated. Nervous system side effects are the most common, including drowsiness, dizziness, unsteadiness when walking, **fatigue**, and vision changes (double-vision, blurred vision). These side effects appear to be dose-related, and some patients may develop tolerance to these effects after the first several weeks of therapy. If these side effects persist or worsen, a physician should be notified. Other side effects that occur less frequently are irritability, dyspepsia, mood changes, memory loss, difficulty concentrating, slurred speech, and impotence. Elderly patients may be more sensitive to the side effects of gabapentin.

Interactions

One of the advantages of gabapentin is that it is not broken down in the body and does not have a lot of drug interaction. Antacids may interfere with the absorption of this medication in the body; they should be taken at least two hours apart. Gabapentin does not effect other commonly used anticonvulsants (for example, phenytoin, carbamazepine, valproic acid, and phenobarbital).

Olga Bessmertny, Pharm.D.

Gallbladder cancer

Definition

Cancer of the gallbladder is cancer of the pear-shaped organ that lies on the undersurface of the liver.

Description

Bile from the liver is funneled into the gallbladder by way of the cystic duct. Between meals, the

gallbladder stores a large amount of bile. To do this, it must absorb much of the water and electrolytes from the bile. In fact, the inner surface of the gallbladder is the most absorptive surface in the body. After a meal, the gallbladder's muscular walls contract to deliver the bile back through the cystic duct and eventually into the small intestine, where the bile can help digest food.

Demographics

About 5,000 people are diagnosed with gallbladder cancer each year in the United States, making it the fifth most common gastrointestinal cancer. It is more common in females than males and most patients are elderly. Southwest American Indians have a particularly high incidence—six times that of the general population.

Causes and symptoms

Gallstones are the most significant risk factor for the development of gallbladder cancer. Roughly 75 to 90 percent of patients with gallbladder cancer also have gallstones. Larger gallstones are associated with a higher chance of developing gallbladder cancer. Chronic inflammation of the gallbladder from infection also increases the risk for gallbladder cancer.

Unfortunately, sometimes cancer of the gallbladder does not produce symptoms until late in the disease. When symptoms are evident, the most common is pain in the upper right portion of the abdomen, underneath the right ribcage. Patients with gallbladder cancer may also report symptoms such as nausea, vomiting, weakness, jaundice, skin **itching**, **fever**, chills, poor appetite, and **weight loss**.

Diagnosis

Gallbladder cancer is often misdiagnosed because it mimics other more common conditions, such as gallstones, cholecystitis, and pancreatitis. But the imaging tests that are utilized to evaluate these other conditions can also detect gallbladder cancer. For example, ultrasound is a quick, noninvasive imaging test that reliably diagnoses gallstones and cholecystitis. It can also detect the presence of gallbladder cancer as well as show how far the cancer has spread. If cancer is suspected, a **computed tomography** scan is useful in confirming the presence of an abnormal mass and further demonstrating the size and extent of the tumor. Cholangiography, usually performed to evaluate a patient with jaundice, can also detect gallbladder cancer.

There are no specific laboratory tests for gallbladder cancer. Tumors can obstruct the normal flow of bile from the liver to the small intestine. Bilirubin, a component of bile, builds up within the liver and is absorbed into the bloodstream in excess amounts. This can be detected in a blood test, but it can also manifest clinically as jaundice. Elevated bilirubin levels and clinical jaundice can also occur with other conditions, such as gallstones.

On occasion, gallbladder cancer is diagnosed incidentally. About one percent of all patients who have their gallbladder removed for symptomatic gallstones are found to have gallbladder cancer. The cancer is found either by the surgeon or by the pathologist who inspects the gallbladder with a microscope.

Treatment team

The main member of the treatment team is the surgeon, since surgical removal of the cancer is the only measure that offers a significant chance of cure. Sometimes the cancer is too advanced such that surgery would be of no benefit. But the patient might suffer from jaundice or blockage of the stomach. In this case, the gastroenterologist or interventional radiologist may be able to provide non-surgical alternatives to address these complications. In limited scenarios, the oncologist or radiation therapist may treat the patient with **chemotherapy** or radiation therapy.

Clinical staging, treatments, and prognosis

Staging of gallbladder cancer is determined by the how far the cancer has spread. The effectiveness of treatment declines as the stage progresses. Stage I cancer is confined to the wall of the gallbladder. Approximately 25% of cancers are at this stage at the time of diagnosis. Stage II cancer has penetrated the full thickness of the wall, but has not spread to nearby lymph nodes or invaded adjacent organs. Stage III cancer has spread to nearby lymph nodes or has invaded the liver, stomach, colon, small intestine, or large intestine. Stage IV disease has invaded very deeply into two or more adjacent organs or has spread to distant lymph nodes or organs by way of **metastasis**.

Early Stage I cancers involving only the innermost layer of the gallbladder wall can be cured by simple removal of the gallbladder. Cancers at this stage are sometimes found incidentally when the gallbladder is removed in the treatment of gallstones or cholecystitis. The majority of patients have good survival rates. Late Stage I cancers, which involve the outer muscular layers of the gallbladder wall, are generally treated in the same way as Stage II or III cancers. Removal of the gallbladder is not sufficient for these stages. The surgeon also removes nearby lymph nodes as well as a portion of the adjacent liver (radical surgery). Survival rates for these patients are considerably worse than for those with early Stage I disease. Patients with early Stage IV disease may

KEY TERMS

Cholangiography—Radiographic examination of the bile ducts after injection with a special dye

Cholecystitis—Inflammation of the gallbladder, usually due to infection

Computed tomography—A radiology test by which images of cross-sectional planes of the body are obtained

Jaundice—Yellowish staining of the skin and eyes due to excess bilirubin in the bloodstream

Metastasis—The spread of tumor cells from one part of the body to another through blood vessels or lymphatic vessels

Pancreatitis—Inflammation of the pancreas

Stent—Slender hollow catheter or rod placed within a vessel or duct to provide support or maintain patency

Ultrasound—A radiology test utilizing high frequency sound waves

benefit from radical surgery, but the issue is controversial. Late Stage IV cancer has spread too extensively to allow complete excision. Surgery is not an option for these patients.

Other therapies

When long-term survival is not likely, the focus of therapy shifts to improving quality of life. Jaundice and blockage of the stomach are two problems faced by patients with advanced cancer of the gallbladder. These can be treated with surgery, or alternatively, by special interventional techniques employed by the gastroenterologist or radiologist. A stent can be placed across the bile ducts in order to re-establish the flow of bile and relieve jaundice. A small feeding tube can be placed in the small intestine to allow feeding when the stomach is blocked. Pain may be treated with conventional pain medicines or a celiac ganglion nerve block.

Current chemotherapy or **radiation therapy** cannot cure gallbladder cancer, but they may offer some benefit in certain patients. For cancer that is too advanced for surgical cure, treatment with chemotherapeutic agents such as fluorouracil (5-FU) may lengthen survival for a few months. The limited benefit of chemotherapy must be weighed carefully against its side effects. Radiation therapy is sometimes used after attempted surgical resection of the cancer to extend survival for a few months or relieve jaundice.

Coping with cancer treatment

After cancer treatment, many patients find that good nutrition, and a strong support system (which may include a support group) improve their quality of life. Treatment team members or hospital social workers can often recommend local resources that can be of assistance to the patient.

Clinical trials

More **clinical trials** are needed to define the role of chemotherapy and radiation therapy after attempted surgical resection of Stage II and III cancer. Some investigators are conducting trials to assess whether extremely radical surgery is beneficial in early Stage IV disease.

Special concerns

After the removal of the gallbladder, patients may experience a temporary change in bowel habits. The bowel movements may be more frequent or more liquid than before surgery. This situation usually resolves within about six months.

Resources

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Kevin O. Hwang, M.D.

Gallium nitrate

Definition

Gallium nitrate is a drug that is used to treat **hypercalcemia**, or too much calcium in the blood. This condition may occur when individuals develop various types of cancer. Gallium nitrate is also known by the common brand name Ganite.

Purpose

The purpose of gallium nitrate is to reduce the level of calcium in a patient's blood. It is a liquid medication that is injected into a person's vein.

Description

Due to the fact that hypercalcemia is a serious condition that can be fatal, it is very important that it is effectively treated. Hypercalcemia is a common complication of cancer, affecting approximately 10–20% of all cancer patients. This condition can affect many systems of the body and has various signs and symptoms. Sometimes, these symptoms may be thought to be associated with the cancer, and therefore the hypercalcemia itself may go undiagnosed.

Symptoms of hypercalcemia include frequent urination, thirst, dizziness, constipation, nausea, vomiting, and disruptions in cardiac rhythm. If severe, this complication can lead to seizure, cardiac arrest, coma, or death.

Hypercalcemia should first be treated with fluids. Doctors should make sure that their patients are properly hydrated, meaning that they have enough fluid in their body. However, fluid treatment alone is usually not effective to treat this condition. Therefore, some physicians may recommend that their patients take gallium nitrate to establish a normal balance of calcium in the blood.

Recommended dosage

The recommended dosage of gallium nitrate differs depending on the patient, and should be determined by a physician. For adults and teenagers, the dosage of this medication is based on body weight/size, and must be calculated by a doctor. The medication is injected into a patient's vein at a slow pace for 24 hours over a period of five days. If a patient's calcium level is still too high, this process can be repeated in two to four weeks. For younger children, up to the age of 12, there are no specific studies to determine the effects of gallium nitrate. Therefore, use and dosage of this medication must be determined by the young cancer patient's personal physician.

While undergoing treatment with gallium nitrate, patients' doctors should check calcium levels at regular intervals. Even if a patient's condition has improved, he or she may still need to be followed closely to make sure that they do not develop hypercalcemia again.

Precautions

Before taking gallium nitrate, there are specific precautions that should be taken to avoid potential complications. Patients should let their physician know if they are allergic to any foods, preservatives or dyes. In addition, patients with certain medical problems, specifically kidney disease, should make sure that their prescribing physician is aware of this, as use of gallium nitrate can exacerbate this condition. Adequate hydration may minimize toxic effects on the kidney.

In addition, use of gallium nitrate has not been studied in pregnant animals or humans. It is not recommended for women who are pregnant or breast-feeding, as it may cause negative side effects.

With regard to children, as stated, there are no studies of gallium nitrate in younger populations. There are also no studies of this medication in the elderly. However, it is not thought that the use of gallium nitrate would cause very different side effects in older people versus younger adults.

Side effects

Individuals who are considering taking gallium nitrate should discuss its use in detail with their physician. This includes talking about the potential benefits versus any potential side effects. Some individuals may experience all, some, or none of these side effects. Some of these side effects may lessen as a person's body gets used to the medication. However, it is important to be aware of these potential side effects because some of them may require medical interventions.

More common side effects:

- blood in the urine
- pain in the bones
- change in urination frequency
- feeling thirsty
- loss of appetite (anorexia)
- weakness of muscles
- feeling nauseous
- diarrhea
- metallic taste in the mouth
- nausea and vomiting
- decrease of phosphate levels in the blood

Less common side effects:

- cramps in the abdomen
- a feeling of confusion
- muscle spasms

Rare side effects:

- excessive **fatigue** or weakness

KEY TERMS

Cancer—One cell that grows out of control in the body and subsequently invades nearby cells and tissue.

Ganite—The commonly used brand name for gallium nitrate.

Hypercalcemia—Excessive or increased calcium in the blood. Often a complication of cancer.

Interactions

Patients should tell their physician if they are taking any other medications on a regular basis, especially the ones listed below, as they could cause a negative interaction if taken with gallium nitrate.

- certain medications taken for infections
- cisplatin
- medications for pain that contain acetaminophen or aspirin
- cyclosporine
- deferoxamine
- some medications for treatment of arthritis
- lithium
- methotrexate
- pencillamine
- gentamicin
- amphotericin B
- "nephrotoxic agents"

Tiffani A. DeMarco, MS

Gallium scan

Definition

A gallium scan of the body is a nuclear medicine test that is conducted using a camera that detects gallium, a form of radionuclide, or radioactive chemical substance.

Purpose

Most gallium scans are ordered to detect cancerous tumors, infections, or areas of inflammation in the body. Gallium is known to accumulate in inflamed, infected, or cancerous tissues. The scans are used to determine whether a patient with an unexplained **fever** has an infection and the site of the infection, if present. Gallium scans also may be used to evaluate cancer following **chemotherapy** or **radiation therapy**.

Precautions

Children and women who are pregnant or breastfeeding are only given gallium scans if the potential diagnostic benefits will outweigh the risks.

Description

The patient will usually be asked to come to the testing facility 24–48 hours before the procedure to receive the injection of gallium. Sometimes, the injection will be given only four to six hours before the study or as long as 72 hours before the procedure. The timeframe is based on the area or organs of the body being studied.

For the study itself, the patient lies very still for approximately 30–60 minutes. A camera is moved across the patient's body to detect and capture images of concentrations of the gallium. The camera picks up signals from any accumulated areas of the radionuclide. In most cases, the patient is lying down throughout the procedure. Back (posterior) and front (anterior) views will usually be taken, and sometimes a side (lateral) view is used. The camera may occasionally touch the patient's skin, but will not cause any discomfort. A clicking noise may be heard throughout the procedure; this is only the sound of the scanner registering radiation.

Preparation

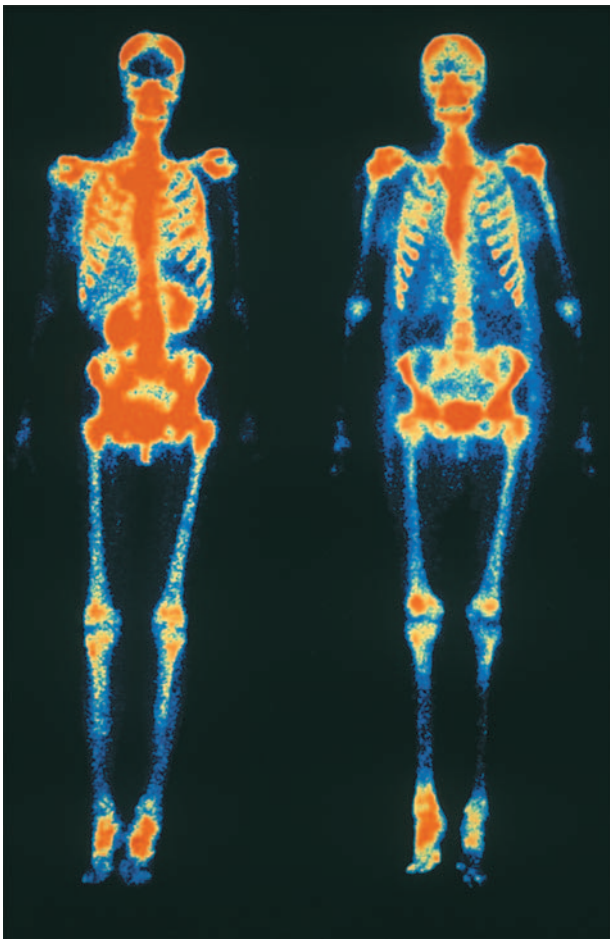
The intravenous injection of gallium is done in a separate appointment prior to the procedure. Generally, no special dietary requirements are necessary. Sometimes the physician will ask that the patient have light or clear meals within a day or less of the procedure. Many patients will be given **laxatives** or an enema prior to the scan to eliminate any residual gallium from the bowels.

Aftercare

There is generally no aftercare required following a gallium scan. However, women who are breastfeeding who have a scan will be cautioned against breastfeeding for four weeks following the exam.

Risks

There is a minimal risk of exposure to radiation from the gallium injection, but the exposure from one gallium scan is generally less than exposure from x rays.



Nuclear medicine scan of the skeleton. A radioisotope, like gallium, is used to produce this image. This scan reveals that lung cancer has spread to ribs and there is osteomyelitis in ankle. *(Copyright Scott Camazine and Sue Trainor, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

KEY TERMS

Benign—Not cancerous. Benign tumors are not considered immediate threats, but may still require some form of treatment.

Gallium—A form of radionuclide that is used to help locate tumors and inflammation (specifically referred to as GA67 citrate).

Malignant—This term, usually used to describe a tumor, means cancerous, becoming worse and possibly growing.

Nuclear medicine—A subspecialty of radiology used to show the function and anatomy of body organs. Very small amounts of radioactive substances, or tracers, are detected with a special camera as they accumulate in certain organs and tissues.

Radionuclide—A chemical substance, called an isotope, that exhibits radioactivity. A gamma camera, used in nuclear medicine procedures, will pick up the radioactive signals as the substance gathers in an organ or tissue. They are sometimes referred to as tracers.

Normal results

A radiologist trained in nuclear medicine or a nuclear medicine specialist will interpret the exam results and compare them to other diagnostic tests. It is normal for gallium to accumulate in the liver, spleen, bones, breast tissue, and large bowel.

Abnormal results

An abnormal concentration of gallium in areas other than those where it normally concentrates may indicate the presence of disease. Concentrations may be due to inflammation, infection, or the presence of tumor tissue. Often, additional tests are required to determine if the tumors are malignant (cancerous) or benign.

Even though gallium normally concentrates in organs such as the liver or spleen, abnormally high concentrations will suggest certain diseases and conditions. For example, Hodgkin's or non-Hodgkin's **lymphoma** may be diagnosed or staged if there is abnormal gallium activity in the lymph nodes. After a patient receives cancer treatment, such as radiation therapy or chemotherapy, a gallium scan may help to find new or recurring tumors or to record regression of a treated tumor. Physicians can narrow causes of liver problems by noting abnormal gallium activity in the liver. Gallium scans also may be used to diagnose lung diseases or a disease called sarcoidosis, in the chest.

Resources

ORGANIZATIONS

American Cancer Society. 1599 Clifton Road NE, Atlanta, GA 30329. (404) 320-3333. <http://www.cancer.org>.

American College of Nuclear Medicine. PO Box 175, Landisville, PA 31906. (717) 898-6006.

American Liver Foundation. 1425 Pompton Avenue, Cedar Grove NJ 07009. (800) GO LIVER (465-4837). <http://www.liverfoundation.org>.

Society of Nuclear Medicine. 1850 Samuel Morse Drive, Reston, VA 10016. (703) 708-9000. <http://www.snm.org>.

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Ganciclovir *see* **Antiviral therapy**

Gastric cancer *see* **Stomach cancer**

Gastrinoma *see* **Zollinger-Ellison syndrome**

Gastrointestinal cancers

Definition

Gastrointestinal (GI) cancers include cancer of the esophagus, stomach, small intestine, colon, rectum, and anus as well as cancers of the liver, pancreas, gallbladder, and biliary system.

Description

The GI tract, or digestive tract, starts from the oral cavity (mouth) and proceeds to the esophagus, the stomach, the duodenum, the small intestine, the large intestine (colon and rectum), and the anus. It processes all the food consumed. Along the way through the tract, food is digested, nutrients and water are extracted, and waste is eliminated from the body in the form of stool and urine. Cancer can affect any of the gastrointestinal organs. The National Cancer Institute estimates that 25% of all cancers are gastrointestinal, with the majority of these occurring in the colon and rectum (colorectal cancers). The next sites most commonly affected by GI cancers are the pancreas, stomach, liver, and esophagus. A brief overview of GI cancers follows; the reader should refer to other specific encyclopedia entries shown in bold for more comprehensive information on these cancers and their treatment. The reader should also note that the overview below does not discuss oral cavity cancers. Those cancers are also discussed in individual entries.

Types of cancers

Esophageal cancer

The esophagus is a muscular, hollow tube that carries food from the oropharynx (area behind mouth and soft palate) to the stomach. It consists of several layers. **Esophageal cancer** usually develops in the inner layer cells and grows outward. There are two major types of esophageal cancer. The first occurs in the cells found in the lining of the esophagus (squamous cells), and the cancer is called squamous cell carcinoma. It can develop anywhere along the entire length of the esophagus and represents approximately half of all reported esophageal cancers. The second type of cancer known to occur in the esophagus is an adenocarcinoma, which is cancer of the glandular cells that line the inside of organs. Adenocarcinoma occurs near the stomach entrance and may be associated with a condition known as **Barrett's esophagus**. This is a disorder in which the lining of the esophagus undergoes cellular changes as a result of chronic irritation and inflammation resulting from a backwash of acidic stomach gastric juices. Esophageal **adenocarcinomas** cannot develop unless squamous cells have been transformed by the acid reflux of the stomach juices. The American Cancer Society (ACS) predicted the occurrence of approximately 12,300 new cases of esophageal cancer in 2000 which will result in some 12,100 deaths in the United States.

Stomach cancer

Stomach cancer is also called gastric cancer. The stomach is located in the upper abdomen under the ribs. It is the most expandable organ of the digestive system. Food reaches the stomach from the esophagus and is broken down by gastric juices secreted by the stomach. After leaving the stomach, partially broken down food passes into the small intestine and afterwards into the colon (first part of the large intestine). In cancer of the stomach, cancerous cells are found in the tissues of the stomach and this cancer can develop anywhere in the organ. It may grow along the stomach wall into other organs such as the esophagus or small intestine. Or it may go through the stomach wall and invade the nearby lymph nodes or organs such as the liver, pancreas, and colon. And it may also spread to more distant organs, such as the lungs, the lymph nodes located above the collar bone, and the ovaries. The major type of stomach cancer is adenocarcinoma (90%). Approximately 24,000 new cases of stomach cancer are diagnosed per year in the US. The number of cases, as well as the death rate, have declined significantly over the past several decades, but it is still the seventh leading cause of cancer deaths. A cure is possible if the cancer is found before spreading to other organs. Unfortunately, the early symptoms are not very noticeable, and by the time stomach cancer is diagnosed, it has in many cases already metastasized.

Liver cancer

The liver is one of the largest organs in the body. In normal adults, it weighs about three pounds and is located in the upper right side of the abdomen, under the right lung and rib cage. It plays a major role in

Gastrointestinal cancers

Cancer	Types
Esophageal cancer	Squamous cell carcinoma
	Adenocarcinoma
Stomach cancer	Adenocarcinoma
Liver cancer	Angiosarcoma
	Hepatoblastoma
	Cholangiocarcinoma
	Hepatocellular carcinoma (hepatoma)
Gallbladder cancer	Adenocarcinoma
	Squamous cell carcinoma
	Carcinosarcoma
	Small cell (oat cell) carcinoma
Pancreatic cancer	Adenocarcinoma
	Insulinoma
	Gastrinoma
	Glucagonoma
	Vipoma
	Somatostinoma
	Acinar cell carcinoma
	Cystic tumors
	Papillary tumors
	Pancreatoblastoma
Colorectal cancer	Adenocarcinoma
	Carcinoid tumors
	Gastroinstestinal stromal tumors
	Lymphomas
Anal cancer	Squamous cell carcinoma
	Basal cell carcinoma
	elanoma
	Adenocarcinoma

digestion, in the transformation of food into energy and in filtering and storing blood. It is also responsible for processing nutrients and drugs, producing bile, controlling the level of glucose (sugar) in the blood, detoxifying blood, and regulating blood clotting. In cancer of the liver, cancerous cells are found in the tissues of the liver. Primary liver cancer is cancer that starts in the liver. As such, it is different from cancer that starts somewhere else and spreads to the liver. Liver cancer is a rare form of GI cancer in the United States with only about 15,000 new cases diagnosed in 2000. Primary cancers of the liver and of the bile ducts are far more common in Africa and Asia than in America, where they only represent 1.5% of all cancer cases. The highest occurrence rate is in Vietnamese men (41.8 per 100,000), probably a result of the high incidence of viral hepatitis infections in their country. Asian-American groups also have higher liver cancer incidence rates than the Caucasian population. Liver cancer mortality rates calculated for populations for which statistics are available are highest in China.

There are four main types of liver cancer: angiosarcoma, a rare type of cancer that starts in the blood vessels of the liver; hepatoblastoma, another rare type of liver cancer occurring chiefly in young children; cholangiocarcinoma, which starts in the bile ducts and accounts for approximately 13% of liver cancers; and finally, hepatocellular carcinoma, also known as hepatoma. The most common liver cancer is hepatocellular carcinoma which accounts for approximately 84% of liver cancers. As is the case with stomach cancer, liver cancer is hard to diagnose early because there are seldom any clear-cut symptoms.

However, some diseases have been identified as liable to increase a person's risk of getting liver cancer. They include: hepatitis B, hepatitis C, cirrhosis of the liver, exposure to certain chemicals such as aflatoxin (a substance made by a fungus in tropical regions and that can infect wheat, peanuts, soybeans, corn, and rice), vinyl chloride, thorium dioxide, anabolic steroids, arsenic, and birth control pills (of a type no longer prescribed).

Gallbladder cancer

The gallbladder is a pear-shaped organ located just under the liver in the upper abdomen. Its role in digestion is to store and release the bile produced by the liver into the stomach to help break down fat. In **gallbladder cancer**, the cancer cells develop in the tissues of the gallbladder. Several types of cancer can occur, such as adenocarcinoma, squamous cell carcinoma, carcinosarcoma and small cell (oat cell) carcinoma, all of them uncommon. Approximately 6,000 to 7,000 new cases are diagnosed per year in the U. S., affecting women twice as often as men and occurring mostly in the elderly.

Pancreatic cancer

The pancreas is a tongue-shaped glandular organ lying below and behind the stomach. It consists of two areas, the exocrine and endocrine regions. The endocrine pancreas secretes the hormones insulin and glucagon, which regulate blood sugar. The exocrine pancreas secretes pancreatic juice into the small intestine. The juice contains enzymes that break down fats and proteins so that the body can use them. In pancreatic cancer, the cancer can develop either in the cells that secrete the pancreatic juice (exocrine pancreatic cancer) or in the cells that release the hormones (endocrine pancreatic cancer). Exocrine pancreatic cancer is much more common than endocrine. Several types can develop, the majority being various types of carcinomas. The American Cancer Society predicted that, in 2000, about 28,300 people in the U. S. will be diagnosed with this type of cancer and that approximately 28,200 will die of the disease. Pancreatic cancer is the fourth leading cause of cancer death in men and women. Because the pancreas is located deep inside the body, it cannot be felt during a routine physical exam, and no tests are presently available to allow early detection.

Colorectal cancers

The colon, the first part of the large intestine, extends from the end of the small intestine to the rectum. The colon has four major divisions. The first is called the ascending colon, it starts where the small intestine attaches and extends upward on the right side of the abdomen. The second part is the transverse colon and it extends across the body to the left side where it joins the third section, called the descending colon, which continues downward on the left side. The fourth part of the colon is the sigmoid colon, which joins the rectum. The rectum joins the anus, where stool passes out of the body.

Each of the divisions of the colon and rectum has several layers of tissue. Colorectal cancers usually start in the innermost layer and can grow through some or all of the other layers. Colorectal cancers are common, and occur more frequently in people over the age of 50. The ACS estimated that in 2001 in the U. S., about 46,000 new cases of **colon cancer** will be diagnosed in men, and about 52,000 cases in women. For rectal cancers, the ACS estimates that about 21,000 men and 16,000 women will be diagnosed in 2001. The number of new colorectal cancer cases and reported deaths have declined in recent years due to improved screening and diagnostic methods. Colorectal cancers are highly treatable when detected early, but the symptoms are often not obvious in early stages.

Over 95% of colorectal cancers are adenocarcinomas. Other, less common types of colorectal cancers are: carcinoid tumors, which develop from the hormone-producing cells of the intestine, gastrointestinal stromal tumors, which start in the connective tissue and muscle layers located in the wall of the colon and rectum, and lymphomas, which are cancers of the immune system cells that usually occur in the lymph nodes but may also start in the colon.

Anal cancer

The anus has several types of tissues. Each type of tissue also contains several types of cells and cancer can develop in each of these kinds of tissues. Approximately half are squamous cell carcinomas. This type of cancer is found in the surface cells that line the anus and most of the anal canal. Another 15% of anal cancers consist of adenocarcinomas and usually start in glands found in the anus area. The remaining anal cancers are accounted for by basal cell carcinomas and malignant melanomas. **Anal cancer** is usually diagnosed in people over 50. People who have the human papillomavirus (HPV) also have a greater chance of developing anal cancer as well as men who practice anal sex. How treatable the cancer is depends partly on where it starts.

KEY TERMS

Abdomen—A part of the body which lies between the thorax and the pelvis. It contains a cavity (abdominal cavity) which holds organs such as the pancreas, stomach, intestines, liver, gallbladder. It is enclosed by the abdominal muscles and the vertebral column (backbone).

Bile—A greenish-yellow fluid produced by the liver and stored in the gallbladder.

Bile ducts—Passages external to the liver for the transport of bile.

Digestion—The conversion of food in the stomach and in the intestines into substances capable of being absorbed by the blood.

Digestive system—Organs and paths responsible for processing food in the body. These are the mouth, the esophagus, the stomach, the liver, the gallbladder, the pancreas, the small intestine, the colon, and the rectum.

Gastric juice—An acidic secretion of the stomach that breaks down the proteins contained in the ingested food, prior to digestion.

Gland—An organ that produces and releases substances for use in the body, such as fluids or hormones.

Lymph nodes—Small, bean-shaped organs surrounded by a capsule of connective tissue. Also called lymph glands. Lymph nodes are spread out along lymphatic vessels and store special cells (lymphocytes), which filter the lymphatic fluid (lymph).

Lymphatic system—The tissues and organs that produce, store, and carry white blood cells that fight infection. It includes the bone marrow, spleen, thymus, and lymph nodes as well as a network of thin vessels (lymphatic vessels) that carry lymph and white blood cells into all the tissues of the body.

Metastasis—The transfer of cancer from one location or organ to another one not directly related to it.

Ovary—One of two small oval-shaped organs located on either side of the uterus. They are female reproductive glands in which the ova (eggs) are formed.

Small intestine—The part of the digestive tract located between the stomach and the large intestine.

Squamous cells—Flat, thin cells, such as found on the outer layer of the skin.

Stage—The extent to which a cancer has spread from its original site to other parts of the body. A Stage 1 cancer is less advanced than a Stage 4 cancer.

See also Bile duct cancer; Carcinoid tumors, gastrointestinal; Human papilloma virus.

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American Cancer Society (National Headquarters). 1599 Clifton Road, N.E., Atlanta, GA 30329.(800) 227-2345. Web site: <http://www.cancer.org>.

Cancer Research Institute (National Headquarters). 681 Fifth Avenue, New York, NY 10022. (800)992-2623. Web site: <http:://www.cancerresearch.org>.

National Cancer Institute's Cancer Information Service: 1-800-4-CANCER.

OTHER

University of Michigan Gastrointestinal Cancer Clinic Web site: <http://www.cancer.med.umich.edu/clinic/giclinic.htm>.

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G-CSF *see* **Filgrastim**

Gastrointestinal complications

Description

Constipation, fecal impaction, bowel obstruction, and **diarrhea** are common gastrointestinal complications faced by cancer patients due to either their cancer or the treatment of it. The seriousness of these complications varies from mildly uncomfortable to life threatening.

Constipation is the slow and infrequent passage of small, dry bowel movements through the large intestine. Unpleasant and sometimes painful, constipation often causes people to strain while trying to have a bowel movement. However, constipation itself is generally not life threatening; however, fecal impaction can be.

Fecal impaction is the collection of hard, dry stool in the colon or rectum that can't be excreted. Patients with fecal impaction may or may not experience the typical gastrointestinal symptoms usually associated with constipation, such as cramping and pressure. For example, if the impaction is pressing on a nerve, there may be back pain. If the impaction is pressing on the urethra or bladder, there may be an increase or decrease in urination. There may be nausea and abdominal pain, as well as stool that leaks out when the patient coughs and explosive diarrhea, which is the result of stool moving around the impaction. When movement of the diaphragm is restricted due to abdominal distention (swelling of the abdomen), the patient may not be getting enough oxygen. Breathing, heart, and circulation problems may develop, such as dizziness, hypotension (low blood pressure), hypoxia (a lack of oxygen to the brain), and angina. If left untreated, fecal impaction can cause death.

Bowel obstruction, as defined by the National Cancer Institute, is "a partial or complete blockage of the small or large intestine by a process other than fecal impaction. Classified by type, cause, and location, bowel obstructions can be caused by tumors inside or outside of the bowel, as well as the development of scar tissue after surgery. Patients with colostomies have an increased risk of becoming constipated. Therefore, they need to be especially proactive and report any signs of constipation to their physicians in order to avoid developing bowel obstruction.

Diarrhea is loose, watery stool, which results in abdominal cramps and frequent trips to the bathroom. For cancer patients, diarrhea tends to be especially bothersome. It can affect their eating patterns, as well as cause them to become dehydrated and lose weight. Although it can usually be managed, it sometimes leads to life threatening problems.

Causes

Constipation and fecal impaction

Constipation can have many causes. It can be a symptom of cancer or the result of a growing tumor. It can be linked to certain cancer treatments as well. Sometimes the medications given to cancer patients, such as **opioids** for pain, diuretics, or **chemotherapy** drugs, can cause

constipation. Medications prescribed for anxiety and **depression**, not to mention the depression itself, can be the culprits, too. Patients may find it difficult or painful to move and may put off going to the bathroom. Physical illness, exacerbated by depression, can also alter eating habits, resulting in dietary changes that aren't healthy, such as drinking too little water or not eating enough. In addition, certain muscle and nerve damage, such as **spinal cord compression** from a tumor, can lead to a loss of muscle tone in the bowel, making it difficult for a patient to complete a bowel movement. Environmental factors can worsen constipation. For example, patients who are in unfamiliar surroundings, or need assistance getting to the bathroom, or use a bedpan may have difficulty relaxing and this may affect their ability to defecate. Treating cancer patients with dignity and allowing them as much privacy as possible can be very helpful in these situations.

The National Cancer Institute has identified five major factors that can lead to fecal impaction:

- Opioid pain medications
- Inactivity over a long period of time
- Changes in diet
- Mental illness
- Long-term use of **laxatives**

Oddly enough, using laxatives over a long period of time actually contributes to the development of constipation and fecal impaction, because the higher doses necessary to do the job "make the colon less able to signal the need to have a bowel movement," according to the National Cancer Institute. It may be difficult for cancer patients to avoid repeated bouts of constipation during their cancer treatment, especially if they are taking opioids for pain. However, patients should talk with their physicians about the specific preventative measures that would be the most suitable for them. Every effort should be made to avoid fecal impaction.

Bowel obstruction

According to the National Cancer Institute, "a bowel obstruction may be caused by a narrowing of the intestine from inflammation or damage of the bowel, tumors, scar tissue, hernias, twisting of the bowel, or pressure on the bowel from outside the intestinal tract." Most bowel obstructions, usually due to scar tissue and hernias, occur in the small intestine. Tumors, volvulus (twisting of the bowel), or diverticulitis account for most of the bowel obstructions in the large intestine. Cancers of the colon, stomach, and ovary are the ones that most frequently cause bowel obstructions. When lung and breast cancers spread to the abdomen, they too can cause bowel obstructions. Ripamonti and colleagues reported in the *Annals of Oncology* in 1993 that having abdominal surgery or abdominal radiation puts patients at a greater risk of developing a bowel obstruction.

Diarrhea

Most often when cancer patients have diarrhea, the cause is related to their cancer therapy (i.e., chemotherapy drugs, especially fluoropyrimidines or **irinotecan**, **radiation therapy**, or surgery). Intestinal surgery, for example, can cause diarrhea by negatively affecting the way the bowel functions. Chemotherapy drugs, which can alter the way food is broken down and absorbed in the small intestine, can cause indigestion and diarrhea. According to Tuchmann and Engelkind, the stress and anxiety associated with cancer diagnosis and treatment can also cause diarrhea. Unfortunately, antibiotic therapy to treat infection, as the National Cancer Institute points out, "can cause inflammation of the lining of the bowel, resulting in diarrhea that often does not respond to treatment." In other cases, the cause can be directly tied to the patient's diet or use of laxatives. Severe diarrhea may result from concurrent chemotherapy and radiation therapy.

Treatments

Constipation and fecal impaction

A physician can diagnosis the causes of constipation by performing a physical examination and reviewing a patient's medical history. The patient's stool can be tested for the presence of blood, which is done by asking the patient to provide a sample. In some cases, the physician might suspect that constipation has progressed to fecal impaction. In that case, an examination might include x-rays of the abdomen or chest, blood tests, and an electrocardiogram, which is a painless test that shows the activity of the heart. Another way to check for fecal impaction is to perform a rectal examination, which involves the physician inserting a lubricated, gloved finger into the rectum. If there is an impaction, there may be some discomfort; however, in general, the worst part of this examination is the embarrassment some people might feel.

A **colonoscopy** might be scheduled to see if cancer is present or to simply rule it out. A colonoscopy takes about thirty minutes to complete and is performed in a clinic or hospital setting. It is relatively painless, because patients are given a sedative and/or pain medicine. By inserting a flexible lighted tube into the patient's anus, the physician is able to see the entire large intestine all the way to the lower end of the small intestine.

Treatments options for patients with constipation may include a combination of preventative measures.

Patients will probably be advised to keep track of their bowel movements in a journal. If they are too ill to do so, their caregivers may be asked to perform the task on their behalf. When the patient is trying to defecate, caregivers should be careful to respect their privacy, allowing them enough time and space to encourage success. Some patients find it helpful to run water in the sink or tub; the sound relaxes them and creates a sound barrier. If it is not contraindicated, patients may be advised to add fiber to their diets. Patients may be referred to nutritionists who are familiar with addressing the needs of cancer patients and can create individualized meal plans based on a patient's medical profile.

Adequate fluid intake is critical for patients prone to developing constipation, as well as fecal impaction. Patients may be asked to reduce their use of laxatives. In addition, patients should seek the approval of their physicians before they take any over-the-counter medications. According to the National Institute of Cancer, "impactions are usually treated by moistening and softening the stool with an enema." However, a physician needs to be consulted before an enema is given, because too many enemas can damage the bowel. Nonstimulating bowel softeners may be needed. In some cases, it may be necessary for the fecal material to be manually removed by a physician, although it is understandable that many patients may dislike the thought of it.

Bowel obstruction

To make a diagnosis of bowel obstruction, the physician will need to perform a physical exam to determine if the patient has abdominal pain, gas, or stool in the bowel. The physician will most likely want to draw blood in order to check for infection and body chemistry imbalances. If an obstruction is diagnosed, a **barium enema** may need to be performed to ascertain its location.

Bowel obstruction can be classified into two categories: acute (short term) and chronic (long term). Patients with acute bowel obstruction must be monitored carefully. If their condition cannot be stabilized, it may necessary to insert a lubricated nasogastric tube through the patient's nose and esophagus until it reaches the stomach. Many patients find this procedure initially unpleasant, which is understandable. It is a brief procedure, but it causes many patients to gag and, in some cases, vomit. Some patients may respond better to a tube inserted in their rectum to relieve the pressure. The purpose of inserting the tube is to reduce the patient's swelling, gas, and excess fluid; however, surgery may be unavoidable, if the obstruction worsens and completely blocks the bowel. The insertion of a stent may be required in patients with advanced cancer, if the obstruction cannot be removed through surgical means.

A chronically ill patient may need to have a gastrostomy tube (or feeding tube) inserted through the wall of the abdomen into the stomach. This is done to help the patient eat and to alleviate painful symptoms. A gastroenterologist performs the procedure while the patient is under general anesthesia; therefore, it is completely painless. The tube may need to be temporary or permanent, depending on the patient's condition.

Diarrhea

Many factors can play a part in causing diarrhea, making its treatment challenging. Because severe diarrhea can be very upsetting and even life threatening, physicians will try to establish the cause of the problem as quickly as possible. Patients can expect to be asked a series of questions and to be physically examined. Their vital signs, such as blood pressure and pulse, will be taken and compared to previous readings. The patient may need to provide a stool sample so that it can be tested for the presence of blood or bacteria.

Dietary changes are likely to be suggested. The patient may be given a list of foods to avoid and a list of foods that are acceptable in small quantities. Patients with severe diarrhea may need to monitored closely by their caretakers or admitted to the hospital where intravenous fluids will be administered.

Alternative and complementary therapies

RELAXATION THERAPY Some patients find that relaxation therapy helps them cope with the anxiety associated with cancer treatments and their side effects. A well-established psychogenic modality, relaxation therapy has been said to help cancer patients alleviate pain. When patients are in pain, they tend to tense up. This increases the pain, which causes even more stress. Learning relaxation techniques can help reverse this negative cycle. For example, some patients have found that by utilizing progressive muscle relaxation techniques, they are better able to handle physical and emotional pain, such as constipation and anxiety.

COMFORT MEASURES Utilizing comfort measures to help patients heal is grounded in the belief that a patient should be seen as a whole person, not just someone with a disease and symptoms. Those who practice Eastern medicine have traditionally embraced this holistic approach, which considers the patient's mind, body, and spirit. Indeed, many Eastern philosophies have begun to greatly influence Western society. Some physicians have begun to change their personal philosophies to incorporate holistic concepts in their therapeutic handling of pain. For example, some cancer patients suffer not only from

KEY TERMS

Angina—Angina is chest pain that occurs when the heart muscle doesn't get enough blood.

Diverticulitis—Diverticulitis is inflammation of an abnormal pouch (diverticulum) in the intestinal wall.

physical pain, but they also feel anxious and show signs of depression. In an article published by the *New England Journal of Medicine*, Dr. Campion promotes comfort measures as a way to help alleviate depression, recognizing that a person's state of mind affects his or her physical health. Comfort measures that embrace dignity, such as showing the patient kindness and respect, go a long way to promote healing. Patients with diarrhea, for example, can benefit from comfort measures that include a bedside commode, frequently changed sheets, and adjustable beds.

ACUPUNCTURE Over 10,000 acupuncture and Oriental medicine practitioners currently practice in the United States. In a 1997 consensus statement issued by the National Institutes of Health, acupuncture was recognized as being an effective treatment for pain and nausea. It has also been used successfully to treat bowel obstructions. Developed by the Chinese as far back as 3000 B.C., acupuncture is thought to correct an imbalance of energy flow in the body. The technique involves inserting fine, sterile needles into a person's energy points, sometimes referred to as meridians. Some people fear acupuncture because they think the procedure will be painful, but in actuality it is not painful and tends to relax many people. Some people even fall asleep during the procedure.

Not everyone agrees on how acupuncture works, but research has shown that acupuncture increases the body's electromagnetic flow, which could cause the release of endorphins, the body's natural painkillers. Acupuncture is performed in a clinical setting. Patients interested in receiving acupuncture treatments should talk with their doctors to obtain suitable referrals to reputable, well-trained medical practitioners.

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Lee Ann Paradise

Gefitinib

Definition

Gefitinib, which is also known as Iressa, is an anticancer drug used to inhibit the growth of lung cancer cells and reduce the size of a cancerous tumor.

Purpose

Gefitinib is used as a single agent for the treatment of advanced **non-small cell lung cancer** that has advanced or failed to respond to other kinds of treatment. It is not suitable for use as an initial treatment, but may help to shrink tumors by as much as 10% when used as a third-line therapy in patients with advanced non-small lung cancer.

Description

In May 2003, gefitinib was approved for use in the United States under the U.S. Food and Drug Administration's (FDA) accelerated approval program. Generally speaking, before the FDA approves a drug for use, a great deal of data regarding the safety, efficacy, and quality of the drug is usually compiled. In fact, it is typical for the FDA to review thousands of pages of data about a medicine under consideration for approval. One of the reasons for this is the FDA's extremely strict approval process, an approval process that is, in fact,

among the strictest in the world. FDA approval means that the regulators have decided that the new drug's potential benefits outweigh its risks. When a drug is approved under the accelerated program it is done so because, as Mark B. McClellan, M.D. and FDA Commissioner states, the "FDA believes it is critical for patients to have many safe and effective treatment options available to them in their battles against disease."

In a 2004 article published in the *Pfizer Journal* entitled, "Enhancing Pharmaceutical Safety," Dr. Stephanie Crawford, a member of the FDA's Drug Safety and Risk Management Advisory Committee, said the following: "Approval of a drug as safe is not a blanket statement that it is without risk. It means that the risk is acceptable." Drawing on information provided by the FDA, it was further stated in the article that "the decision to approval a medicine involves consideration of the disease: a product to treat a life threatening condition may be approved even if it presents more of a certain risk, because its potential benefits are so great." In other words, the approval of a valuable cancer drug associated with an adverse side effect might be seen as more acceptable than the approval of an allergy medicine with the same side effect. As was further stated in the article, "The value of the medicine has to be seen in the context of its benefits, its known adverse effects, the severity and reversibility of these effects, and the availability of other medications for that person."

As the FDA cautiously stated in 2003, "The mechanism by which Iressa [gefitinib] exerts its clinical benefit is not fully understood. However, Iressa was developed to block growth stimulatory signals in cancer cells. These signals are mediated in part by enzymes called tyrosine kinases. Iressa blocks several of these tyrosine kinases, including the one associated with the Epidermal Growth Factor Receptor (EGFR)." Research has shown that the EGFR is sometimes found in abundance on the surface of cancer cells, causing them to divide excessively. Therefore, by blocking EGFR, it is thought that tumor growth can be thwarted.

However, gefitinib was approved by the FDA, as all drugs approved under the accelerated program, with the condition that further studies would be conducted to measure the drug's clinical benefit. According to the FDA, the drug's sponsor would be required to conduct three studies. One would evaluate gefitinib as a third-line therapy drug and evaluate if it prolonged survival as compared to the best supportive care available. Another study would compare gefitinib to **docetaxel**, which is another approved **chemotherapy** drug. And the third trial would analysis whether gefitinib is effective in reducing cancer symptoms in patients with lung cancer that are resistant to all available chemotherapy treatments. As Dr. McClellan indicated, "the studies are needed to confirm the clinical benefit, understand better which patients benefit, and evaluate long-term safety."

However, on March 4, 2005, Public Citizen in a letter to the FDA petitioned for gefitinib's removal from the market, stating that the study conducted to prove gefitinib's efficacy had failed and that the drug had already been removed from the market in Europe. Furthermore, the use of the drug has been tied to deaths in Japan. Therefore, it is possible that before long the FDA will reclassify gefitinib as an experimental drug.

Recommended dosage

Gefitinib is available in 250 mg tablets. Dosage levels may vary, depending on the needs of the patient. However, patients generally take one 250 mg tablet a day. The tablets should not be crushed or broken and the patient should be certain to drink plenty of fluids throughout the day.

Precautions

Women who are pregnant or may become pregnant should not use gefitinib. Patients receiving gefitinib should not breast-feed their babies during the treatment cycle and for a substantial time after the treatment.

Side effects

This drug has been associated with high toxicity in Japan. There have been reports indicating that using gefitinib caused severe side effects, such as inflammation of the lungs (interstitial **pneumonia**) and difficulty in breathing. Therefore, patients should report any side effects, whether they seem severe or not, to their physician. The most common side effects associated with taking 250 mg a day were:

- skin rash
- diarrhea
- acne
- dry skin
- nausea and vomiting

As reported in *Applied Therapeutics: The Clinical Use of Drugs* the most common side effects were skin related, which went away after the drug was discontinued. The symptoms were managed through the use of steroid creams, antihistamines, or topical or systemic **antibiotics**.

KEY TERM

Public Citizen—Public Citizen defines itself as " a national, nonprofit consumer advocacy organization founded in 1971 to represent consumer interests in Congress, the executive branch and the courts."

Interactions

Gefitinib increases the effect of metoprolol and may increase the risk of bleeding in patients taking **warfarin**. The following drugs may decrease gefitinib's effectiveness:

- cimetidine
- phenytoin
- rifampin
- ranitidine
- sodium bicarbonate

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Lee Ann Paradise

Gemcitabine

Definition

Gemcitabine is a drug that is used to treat advanced stages of pancreatic, lung, and other cancers. Its brand name is Gemzar.

Purpose

Gemcitabine is used to treat pancreatic cancer, particularly when it has metastasized, or spread to other parts of the body (Stage IVB). In combination with the drug **cisplatin**, gemcitabine is the first-line treatment for inoperable, metastasized non-small cell lung cancer. Sometimes it is used to treat cancers of the bladder or breast, or epithelial **ovarian cancer**.

Description

Gemcitabine is a relatively new anticancer drug. It is a type of medicine called a pyrimidine antimetabolite because it interferes with the metabolism and growth of cells. It does this by replacing the pyrimidine deoxycytidine in DNA, thereby preventing the DNA from being manufactured or repaired. As a result, cells cannot reproduce and eventually die.

Gemcitabine was approved by the U.S. Food and Drug Administration (FDA) to treat pancreatic cancer in 1998 and non-small cell lung cancer in 2002. Gemzar may relieve pain and other symptoms of advanced pancreatic cancer and increase survival time by several weeks to two months. Clinical studies of pancreatic cancer are comparing the effectiveness of combination treatments using gemcitabine with fluorouracil (5-FU), cisplatin, streptozocin, or **radiation therapy**. Gemcitabine has activity against metastatic **bladder cancer** and recurrent ovarian cancer, and further **clinical trials** are underway. Gemcitabine is being evaluated for its effectiveness in the treatment of uterine, stomach, laryngeal and hypopharyngeal, and colon and rectal cancers.

Recommended dosage

Gemcitabine is administered by injection over a period of 30 minutes. The dosage and number of administrations depend on a variety of factors, including the type of cancer, body size, the patient's sex, and other concurrent treatments.

Precautions

Gemcitabine may temporarily reduce the number of white blood cells, particularly during the first 10–14 days after administration. A low white blood cell count

reduces the body's ability to fight infection. Thus, it is very important to avoid exposure to infections and to receive prompt medical treatment. Immunizations (vaccinations) should be avoided during or after treatment with gemcitabine. It also is important to avoid contact with individuals who have recently taken an oral polio vaccine. Treatment with gemcitabine may cause chicken pox or shingles (**herpes zoster**) to become very severe and spread to other parts of the body.

Gemcitabine also may lower the blood platelet count. Platelets are necessary for normal blood clotting. The risk of bleeding may be reduced by using caution when cleaning teeth, avoiding dental work, and avoiding cuts, bruises, or other injuries.

Gemcitabine can cause birth defects and fetal death in animals. Therefore, this drug should not be taken by pregnant women or by either the man or woman at the time of conception. Women usually are advised against breast-feeding while taking this drug.

Side effects

Gemcitabine affects normal cells as well as cancer cells, resulting in various side effects. The most common side effects are related to reduction in red and white blood cells and blood platelets. These side effects may include symptoms of infection or unusual bleeding or bruising. Older patients are more likely to suffer from low blood cell counts after treatment.

Flu-like symptoms are common following the first treatment with gemcitabine. Other common side effects of gemcitabine may include:

- nausea
- vomiting
- chills and fever
- constipation
- diarrhea
- loss of appetite (anorexia)
- headache
- muscle pain
- weakness or fatigue
- shortness of breath
- blood in urine or stools
- skin rash
- swelling of the hands, feet, legs, or face
- insomnia

Less common side effects of gemcitabine may include:

KEY TERMS

Deoxycytidine—Component of DNA, the genetic material of a cell, that is similar in structure to gemcitabine.

Metastasis—Spread of cancer from its point of origin to other parts of the body.

Platelet—Blood component that aids in clotting.

Pyrimidine—Class of molecules that includes gemcitabine and deoxycytidine.

Vasculitis—Inflammation of a blood or lymph vessel.

- cough or hoarseness
- lower back or side pain
- painful or difficult urination
- chest, arm, or back pain
- difficulty with speech
- fast or irregular heartbeat
- high blood pressure
- pain or redness at the site of injection
- numbness or tingling in hands or feet
- sores or white spots on lips and in mouth
- hair loss (alopecia)
- **itching**

Some of these side effects may occur or continue after treatment with gemcitabine has ended. Itching, hives, swelling, or a skin rash, particularly if accompanied by breathing problems, may indicate an allergic reaction to gemcitabine. Some researchers have coined the term gemcitabine-induced severe pulmonary toxicity, or GISPT, to describe an inflammatory reaction in the lungs following treatment with gemcitabine. The incidence of GISPT is estimated to range between 0.5% and 5% of patients receiving the drug.

Additional side effects of gemcitabine may be symptoms associated with liver or kidney malfunction. Furthermore, kidney or liver disease may cause gemcitabine to be removed from the body at a slower rate, thus increasing the effects of the drug.

Another potentially fatal side effect of gemcitabine is vasculitis, or inflammation of blood or lymph vessels. A group of physicians in Iowa reported on two cases of women who died of necrotizing enterocolitis resulting from vasculitis associated with gemcitabine treatment for ovarian

cancer. A case of vasculitis in a male patient treated with gemcitabine for bladder cancer was reported in Turkey.

Interactions

Previous treatment with radiation or other anti-cancer drugs can increase the risk of very low blood counts with gemcitabine. Serious problems may develop in areas previously treated with radiation.

Drugs that may interact with gemcitabine, or that may increase the risk of infections while being treated with gemcitabine, include live **vaccines** and **warfarin**. Because some other medications have a tendency to interact with gemcitabine, patients should alert their doctor to any drugs they are taking.

It is also important not to take any medicines containing aspirin during treatment with gemcitabine, since aspirin can increase the chances of excessive bleeding.

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United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

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Gemtuzumab

Definition

Gemtuzumab ozogamicin is a humanized monoclonal antibody produced by recombinant DNA technology that binds specifically to CD33, a protein that is found on the cell surface of most leukemic blasts, the abnormal, cancerous cells in acute myeloid leukemia (also known as **acute myelocytic leukemia**, or AML). It is marketed in the United States under the brand name Mylotarg.

Purpose

Gemtuzumab is a monoclonal antibody used to treat AML that is characterized by expression of the CD33 protein on the cancerous cells, called leukemic blasts. The CD33 protein is found on the surface of the leukemic blasts of about 80% of AML patients. After the gemtuzumab antibody is produced in the laboratory, a chemical reaction is used to link it to an antitumor drug called calicheamicin. About half of the antibody succeeds in acquiring the antitumor drug.

When the antibody-calicheamicin molecule binds to the cancerous cells, both the antibody and the drug are taken into the cell. There the drug binds to the cell's genetic material (deoxyribose nucleic acid or DNA) inducing breaks in the molecule and killing it. Because the antibody carries and delivers the toxic drug to the leukemic blasts targets, gemtuzumab treatment is called antibody-targeted **chemotherapy**.

Gemtuzumab can also be used to induce remission (remove cancerous cells) in AML patients to prepare them for stem-cell transplantation. It is indicated for refractory AML (AML that does not readily yield to treatment). The use of antibody-targeted chemotherapy has been shown to have fewer side effects than traditional chemotherapy courses and does improve the disease-free survival time after transplantation.

Description

Gemtuzumab is a genetically engineered monoclonal antibody linked to an antitumor antibiotic. It was approved by the FDA in 2000 as a method of treating relapsed AML in older patients (over 60 years of age) that are not candidates for other cytotoxic chemotherapy. About 75% of all patients with AML experience a relapse after initial treatment. In **clinical trials** focusing on the treatment of older patients with relapsed AML, gemtuzumab had an overall response rate of 30%, with 16% having a complete response.

Most of the gemtuzumab sequence is derived from human sequences, while about 2% are from mice. The

human sequences were derived from the constant domains of human IgG4 (called "constant" because it is essentially the same for all IgG antibodies) and the variable framework regions of a human antibody. These areas do not bind to the CD33 protein. Using human sequences in this part of the antibody helps to reduce patient **immune response** to the antibody itself and is called humanization. The actual binding site of gemtuzumab to the CD33 protein is from a mouse anti-CD33 antibody. The antibiotic antitumor drug calcheamicin is linked to the antibody in a way that does not interfere with the ability of the antibody to bind CD33.

Gemtuzumab is not currently approved for use in combination with other chemotherapy drugs or treatments. However, clinical trials that combine the drug with **cytarabine**, **fludarabine**, total-body irradiation, as well as other cancer treatments, are ongoing.

Recommended dosage

Gemtuzumab is administered intravenously. In the pivotal clinical trial, the drug was given at a dose of 9 mg/m^2 for two doses that were fourteen days apart.

Precautions

Extreme caution should be used when using gemtuzumab to treat patients with existent liver problems. Animal studies showed that the drug can cause significant harm to the development of a fetus, so it is likely the drug should not be used during pregnancy, and women of childbearing age should avoid pregnancy while on the drug. Because of the adverse effects of calicheamicin on DNA, the drug greatly reduced fertility in animal studies for males, but not females.

Side effects

A severe side effect of gemtuzumab treatment is a depletion of various types of cells in the bone marrow, including those that make white and red blood cells, a condition known as myelosuppression. Because CD33 is expressed on a patient's normal bone marrow cells, as well as on the surface of the abnormal leukemic blasts, the treatment eliminates both normal and cancerous cells. This results in severe reduction of the circulating blood cells normally produced by the bone marrow, including red blood cells (**anemia**), white blood cells (**neutropenia**), and clotting cells (thrombocytopenia). These conditions are treated with blood transfusions. However, the population of all these cells will rebound after clearance of gemtuzumab because the precursor to cells of the bone marrow, called pluripotent hematopoietic stem cells, do not express CD33 and will restore the various cell populations.

Gemtuzumab can produce a postinfusion symptom complex of **fever** and chills, and less commonly, low blood pressure and labored breathing during the first 24 hours after administration. Some patients developed severe liver function abnormalities, which were generally transient and reversible. The most common side effects were fever, chills, nausea, vomiting, thrombocytopenia, neutropenia, asthenia (loss of strength or energy), **diarrhea**, abdominal pain, headache, and **stomatitis** (inflammation of the lining of the mouth).

KEY TERMS

Antibody—A protective protein made by the immune system in response to an antigen, also called an immunoglobulin.

Blasts—A type of immature cell that lacks some of the outward characteristics of the mature cell. In AML, the cancerous cells are leukemic blasts.

Calicheamicin—An anti-tumor drug that binds to DNA within the tumor cells, causing breaks in the strands and killing the cell.

IgG—Immunoglobulin type gamma, the most common type found in the blood and tissue fluids.

Humanization—Fusing the constant and variable framework region of one or more human immunoglobulins with the binding region of an animal immunoglobulin, done to reduce human reaction against the fusion antibody.

Monoclonal—Genetically engineered antibodies specific for one antigen.

Myelosuppression—Reduction in the number of the cells of the bone marrow, which leads to reduction of many other circulating blood cells that are produced by the marrow.

Interactions

There have been no formal drug interaction studies done for gemtuzumab.

See also Monoclonal antibodies.

Michelle Johnson, M.S., J.D.

Genetics of cancer *see* **Cancer genetics**

Genetic testing

Definition

Genetic testing is a process which involves examining individuals' genetic material for the presence of a change that indicates why they may have developed a disease or disorder. Genetic testing may also tell patients if they are at increased risk for developing a disease such as cancer in the future, but currently do not have any symptoms of that particular disease.

Description

Genetic testing is usually done by taking a sample of a person's blood. The changes in the genetic material that can be detected by this testing vary in size. Sometimes parts or even entire chromosomes may be altered or missing completely. Other times, a mutation is present on a gene that causes it to malfunction. One type of mutation is known as a hereditary mutation. Hereditary mutations may also be called germline mutations because they are found in all the cells of a person's body, including the reproductive or germ cells, the sperm for a male and the egg for a female. This is why hereditary mutations can be inherited, or passed from a parent to a child. Genetic testing often looks for the presence or absence of these types of mutations in genes.

Genes and cancer

Cancer is defined as one cell that grows out of control and subsequently invades nearby cells and tissue. There are several steps involved in the process that causes a normal cell to become malignant (cancerous). It is believed that different genes play a role in this specialized process. Oncogenes typically promote or encourage cell growth. However, if they are overexpressed or mutated, they may cause cancer to arise. Tumor-suppressor genes, when working properly, prevent cells from growing too quickly or out of control. They are often compared to brakes in a car. If these genes cannot perform their function because of the presence of a mutation, cells may grow out of control and become cancerous. Finally, cancer may also be caused by faulty DNA repair genes. These genes usually correct the common mistakes that are made by the body as the DNA copies itself, a normally occurring process. However, if these genes can't correct mistakes, the mistakes may accumulate and lead to cancer.

It is very important to remember that while all cancer is genetic, or caused by changes in genes, just a small amount of cancer is hereditary, or passed from parent to child. It is thought that only about 5-10% of cancer falls into this category. Therefore, the majority of cancer is not hereditary. Most cancer is due to other causes, such as environmental exposures. Usually it is very difficult to determine the exact cause of cancer that is not known to be the result of an altered gene.

Identifying at-risk individuals and families for hereditary cancer

Although scientists have identified genetic tests for common cancers, like breast and **colon cancer**, genetic testing is not an option that should be offered to all people with cancer, or even to those who may have cancer in their family. This is primarily due to the fact that most cancer does not run in families. Therefore, genetic testing will not be helpful for many people. In order to determine those who may benefit from undergoing genetic testing for cancer, health care providers need to be aware of certain aspects of an individual's personal and family history of cancer.

A person who is thinking about having a genetic test for cancer often meets with a genetic counselor, a specially trained health care provider. When a patient meets with a genetic counselor, the counselor will ask the patient about their personal and family history of cancer. The counselor will also draw a very detailed family tree, also known as a pedigree. The counselor will then examine the family tree to determine if there are certain ''clues'' that the cancer may be hereditary.

The clues that may be observed in a family tree are listed below, with **breast cancer** used as an example.

- Multiple relatives in more than one generation with the same type of cancer, or related cancers. For example, a grandmother, mother and daughter with breast cancer. Or, relatives with both breast and **ovarian cancer**.
- Cancer occurring in the family at younger ages than is typically observed in the general population. For example, breast cancer usually occurs in women as they get older, most commonly in their 60's to 70's. However, in families that may have an alteration in a gene increasing their risk for developing breast cancer, the disease may occur in women at much younger ages.
- Cancer that occurs in paired organs. For example, breast cancer that occurs in both of a woman's breasts. This is also called bilateral breast cancer.
- Development of more than one type of related cancer in the same person within a family. For example, a female relative with both breast and ovarian cancer diagnosed at young ages.
- Specific ethnic background. Mutations in certain cancer susceptibility genes may be more likely to occur in

individuals of specific ethnic backgrounds. For this reason, it is very important that a complete family tree includes the country where a person's relatives originally lived.

If a genetic counselor or other health care provider observes one or more of the above features in an individual's family tree, he or she may talk about the option of genetic testing with the patient. In the case of cancer genetic testing, it is only offered to a patient if there are options available to screen for the certain cancer and detect it early, or to possibly prevent it from occurring at all.

The process of genetic testing

The process of genetic testing for genes that may increase risk for cancer is different from other medical tests. Genes involved in cancer are called cancer susceptibility genes. If a mutation is identified in one of these genes, it does not reveal that a person has cancer, but rather whether an individual has an increased risk to develop cancer in the future. In addition, if the person undergoing genetic testing has already had cancer, genetic testing may tell them whether they are at increased risk for developing cancer again. However, the risk for developing cancer is not 100%. The likelihood that a person will develop cancer if they carry an altered gene is called penetrance. Penetrance may differ even among relatives in the same family, and the reasons are not well understood. For example, a mother with a mutation in a cancer susceptibility gene may never develop cancer, but may pass this mutation on to her daughter, who is then diagnosed with cancer at a young age.

For a family in which an inherited mutation has not been previously identified, it is best to begin genetic testing by obtaining a blood sample from a person who has had cancer at a young age. From this blood sample, scientists will be able to extract some DNA. There are a number of different ways that they can then look at the DNA to determine if a mutation is present. The most common is known as sequencing, whereby the chemical sequence of a patient's DNA is compared to DNA that is known to be normal. Scientists will look for any differences, such as missing or extra pieces of DNA in the patient's gene.

Testing can be very expensive and it may take several weeks or months to obtain results. Also, insurance companies will sometimes not cover the cost of testing. Some families are able to participate in research studies where genetic counseling and testing is offered at a lower cost or free of charge.

Categories of results

A positive result indicates the presence of a genetic mutation that is known to be associated with an increased risk for developing cancer. Once this kind of mutation has been found in an individual, it is possible to test this person's relatives, like their children, for the presence or absence of that particular mutation. This testing can be done in a relatively short period of time and provides results that are clearly positive or negative for a particular mutation.

If a relative in a family is tested for a mutation in a cancer susceptibility gene that was previously identified in their family, and they are not found to have this mutation, this type of test result is called a true negative. This means that they did not inherit the mutation in the gene that is the reason why their relative(s)developed cancer. If a person receives a true negative test result, their risk for developing cancer is generally considered to be reduced to that of someone in the general population. Also, because they did not inherit the mutation, they cannot pass it down to any of their children. The term true negative is used to distinguish this test result from a negative or indeterminate result, which is described below.

If the first person tested within a family is not found to have an alteration in a cancer susceptibility gene, this result is negative. However, this result is often called indeterminate. This is because a negative test result cannot completely rule out the possibility of hereditary cancer still being present within a family. The interpretation of this type of result can be very complex. For example, a negative result may mean that the method used to detect mutations may not be sensitive enough to identify all mutations in the gene, or perhaps the mutation is in a part of the gene that is difficult to analyze. It may also mean that a person has a mutation in another cancer susceptibility gene that has not yet been discovered or is very rare. Finally, a negative result could mean that the person tested does not have an increased risk for developing cancer because of a mutation in a single cancer susceptibility gene.

Finally, sometimes mutations are identified in cancer genes and scientists do not know what they mean. They do not know if these types of mutations affect the functioning of the gene and thereby increase a person's risk for cancer, or if they are normal changes in the DNA that just make one person's gene a little bit different from another person's. When this occurs, the genetic counselor may work with the laboratory to determine if future research can be done to find out the meaning of the patient's test result.

In general, a genetic counselor will help a patient to understand the meaning of his or her genetic test result, whether positive, negative, or indeterminate.

Benefits and limitations of undergoing genetic testing for cancer susceptibility genes

There are potential benefits for patients who undergo genetic testing, but there are also possible limitations and risks regarding the information that is obtained. A genetic counselor will discuss these issues in detail with a patient. Before undergoing genetic testing, a patient will also sign a consent form. This is a written agreement indicating that the patient understands the benefits and risks of genetic testing and has made an independent decision to undergo the testing. The informed consent process is a very important part of genetic counseling and testing. With the exception of FAP, where polyps and subsequently colon cancer can occur at young ages or in the teens, the cancers associated with carrying an altered breast or colon cancer susceptibility gene do not typically occur at very young ages. Therefore, genetic testing for mutations in these genes is usually only offered to those men and women who are 18 years of age or older. In addition, individuals who are 18 or older are considered legally able to provide informed consent.

Benefits of participating in genetic testing for alterations in cancer susceptibility genes:

- Results of genetic testing may provide additional information about the increased risk for developing cancer in the future. It may also provide relief from anxiety if a person learns that they do not carry an altered gene.
- If a person finds out that they are at increased risk for developing cancer, they may choose to be screened for this cancer at a younger age and more often than someone without an altered cancer susceptibility gene. Results may also help men and women decide about prophylactic surgery.
- Testing may provide information about cancer risks for children, brothers and sisters, and other relatives.
- Genetic testing may help a person understand why they and/or their family members developed cancer. This may relieve a person from the emotional burden surrounding their cancer diagnosis.

Limitations and risks of participating in genetic testing for cancer susceptibility genes:

- It is possible that the results of genetic testing may be difficult to interpret. Even if a patient receives a positive test result, this does not mean that he/she will definitely develop cancer.
- During the process of undergoing genetic testing, a person may learn information about themselves or their family members. For example, they may learn about an adoption or that an individual is not the biological father of a child. This kind of information may cause strained relationships among relatives.
- Some patients may become sad, angry or anxious if they learn that they have a mutation in a cancer susceptibility gene. If these feelings are very intense, psychological counseling may be helpful.
- Results of genetic testing may place a person at risk for discrimination by health or life insurers, or their employer. There are some laws in effect that provide limited protection to people who undergo genetic testing. The completion of the Human Genome Project, which has mapped all the genes in the human body, will increase the number of genetic tests that are available. Therefore, additional laws need to be passed to completely protect all people who undergo genetic testing from any type of discrimination.

Genes and cancer types

As of 2001,genes have been discovered that are associated with or responsible for several types of cancer, including **Chronic myelocytic leukemia**, **Burkitt's lymphoma**, **retinoblastoma**, **Wilms' tumor**, and breast and colon cancers. The remainder of this entry will focus only on genetic testing for two of the most common cancers, breast and colon cancer.

Breast cancer genetic testing

Breast and ovarian cancer statistics

All women have a risk for developing breast and ovarian cancer during their lifetime. While breast cancer is a common cancer among women in the United States, ovarian cancer is not. Most women are diagnosed with breast or ovarian cancer after the age of 50, and the great majority of cases are not hereditary. But, of the 5-10% of breast and ovarian cancer that does run in families, most is due to mutations in two genes, the BReast CAncer–1 gene (BRCA1) and the BReast CAncer–2 gene (BRCA2). The BRCA1 gene is located on chromosome 17, and was discovered in 1994. The BRCA2 gene is on chromosome 13, and was discovered in 1995.

BRCA1 and BRCA2 genes

BRCA1 and BRCA2 genes are tumor suppressor genes and are inherited in a dominant fashion. This means that children of a parent with a mutation in one of the breast cancer genes have a 50% chance to inherit this mutation. These mutations can be passed from either mother or father, and can be inherited by both males and females. The mutations may be detected by performing genetic testing on a patient's blood sample.

Mutations in these genes are more common in people who are Ashkenazi (Eastern or Central European) Jewish. While these mutations may be more common in this specific population, they can be identified in a person of any ethnic background.

Cancer risks

Females who inherit a mutation in the BRCA1 or the BRCA2 gene have an increased risk for developing breast and/or ovarian cancer over their lifetime. The lifetime risk for breast cancer may be as high as 85%, as compared to about 13% in the general population. The lifetime risk for developing ovarian cancer may be as high as 60%, as compared to 1.5% in the general population. Males who inherit a mutation in one of these genes are also at increased risk for developing certain cancers, including prostate, colon and breast cancer.

Men and women who inherit an alteration in the BRCA2 gene also have an increased risk to develop more rare cancers, such as pancreatic and **stomach cancer**. However, these risks are much lower than those observed for breast, ovarian, and **prostate cancer**.

Screening and prevention options

It is recommended that individuals who are at increased risk for developing breast cancer undergo increased surveillance. This means that they may choose to see their physicians for medical screening tests at an earlier age and more often than they would if they did not have an altered gene. For example, it is recommended that women with an altered BRCA1 or BRCA2 gene undergo mammograms at a younger age than is recommended in the general population. It is also recommended that these women see their doctors more often to do a breast exam and also perform breast self-exams regularly. Because women who have a mutation in BRCA1 or BRCA2 are also at increased risk for developing ovarian cancer, they may also choose to be screened closely for this cancer. This screening involves undergoing a test, called a CA-125, which looks for protein levels in a woman's blood. Women may also undergo a pelvic ultrasound to look at the size and shape of the ovaries to determine if cancer may be growing in that area. It is important to mention that ovarian cancer is a difficult cancer to detect, and these screening methods may not be able to find the cancer at an early stage when a woman can undergo successful treatment.

Men with an altered BRCA1 or BRCA2 gene may also choose to be screened earlier and more frequently for the cancers they are at increased risk to develop. Prostate screening consists of a test called prostate specific antigen (PSA) that looks for protein levels in a man's blood. Men may also undergo an examination by a physician. There are no standard screening recommendations for males who are at increased risk for breast cancer. It is usually recommended that they learn to do breast self-exams and talk with their doctors if they find any changes in their breast tissue.

Researcher examining the genetic code of a sequenced sample of neuroblastoma DNA. *(Copyright Colin Cuthbert, Science Source, Photo Researchers, Inc. Reproduced by permission.)*

Some women at increased risk for developing breast or ovarian cancer may decide to have prophylactic or preventive surgery. This means that they may choose to have their healthy breasts or ovaries removed before cancer develops. However, even the very best surgeon cannot remove all of the breast or ovarian tissue. Therefore, even if a woman has her breasts or ovaries removed preventively, she may still develop cancer in the remaining tissue, but this risk is believed to be small.

Finally, some healthy women who are at increased risk for breast or ovarian cancer may decide to take certain medications that have been shown to reduce risk. As some of these medications have been studied only in the general population, further research is underway to find out how effective these medications are for women with an inherited risk for developing cancer.

Colon cancer genetic testing

Colon cancer statistics

Males and females in the general population have a 6% risk for developing colon cancer over their lifetime, and the average individual is diagnosed in their 60s to

KEY TERMS

Cancer—The process by which cells grow out of control and subsequently invade nearby cells and tissue.

Cancer susceptibility gene—The type of genes involved in cancer. If a mutation is identified in this type of gene it does not reveal whether or not a person has cancer, but rather whether an individual has an increased risk (is susceptible) to develop cancer (or develop cancer again) in the future.

Colonoscopy—A screening test performed with a tube called a colonoscope that allows a doctor to view a patient's entire colon and rectum.

Chromosome—Structures found in the center of a human cell on which genes are located.

DNA repair genes—A type of gene that usually corrects the common mistakes that are made by the body as DNA copies itself. If these genes are mutated and cannot correct these mistakes they may accumulate and lead to cancer.

Gene—Packages of DNA that control the growth, development and normal function of the body.

Genetic counselor—A specially trained health care provider who helps individuals understand if a disease (such as cancer)is running in their family and their risk for inheriting this disease. Genetic counselors also discuss the benefits, risks and limitations of genetic testing with patients.

Hepatoblastoma—A cancerous tumor of the liver. Individuals with FAP have an increased risk for developing this type of tumor at a young age.

Mammogram—A screening test that uses X-rays to look at a woman's breasts for any abnormalities, such as cancer.

Mutation—An alteration in the number or order of the DNA sequence of a gene.

Oncogene—Genes that typically promote cell growth. If mutated, they may encourage cancer to develop.

Pedigree—A family tree. Often used by a genetic counselor to determine if a disease may be passed from a parent to a child.

Penetrance—The likelihood that a person will develop a disease (such as cancer), if they have a mutation in a gene that increases their risk for developing that disorder.

Polyp—A growth that may develop in the colon. These growths may be benign or cancerous.

Prophylactic surgery—The preventive removal of an organ or tissue before a disease such as cancer develops.

Sequencing—A method of performing genetic testing where the chemical order of a patient's DNA is compared to that of normal DNA.

Sigmoidoscopy—A screening test performed with a flexible scope called a sigmoidoscope, that allows a doctor to view a limited portion of a patient's colon or rectum for the presence of polyps.

Tumor suppressor gene—Genes that typically prevent cells from growing out of control and forming tumors that may be cancerous.

70s. Similar to breast and ovarian cancer, most colon cancer does not run in families. However, some colon cancer is hereditary, and may be due to a mutation in a colon cancer susceptibility gene. Three of the more common hereditary colon cancer syndromes are described below.

Familial Adenomatous Polyposis (FAP)

FAP is a syndrome in which individuals develop numerous polyps (growths) in their colon or rectum. This disorder may also be called familial polyposis or Gardner's syndrome. Males or females with FAP often have hundreds of precancerous polyps at young ages, such as when they are teenagers or young adults.

FAP is due to a mutation in a gene called APC. Mutations in this gene are dominantly inherited. In about 80% of families genetic testing performed on a blood sample can find the alteration in the APC gene that is causing this disorder. It is believed that 2/3 of the people with FAP have inherited a mutated gene from their parent. The other 1/3 of individuals with FAP are believed to be new (sporadic) mutations, meaning that the alteration in the APC gene was not inherited from a parent. Individuals with sporadic mutations can pass the mutation on to their children.

Cancer risks

Due to the fact that individuals with FAP develop so many polyps in their colon, there is a very high risk that these polyps, if not removed, will develop into colon cancer. Individuals with FAP may also develop precancerous

polyps in other organs, such as their stomach or small intestine. Young people with FAP may also be at increased risk for developing a tumor in the liver, known as a hepatoblastoma. They are also at increased risk for developing tumors in other parts of the body, such as the thyroid gland or pancreas. Males or females with FAP may also have other manifestations of the disease. For example, they may have cysts or bumps on their skin or on the bones of their legs or arms, or freckle-like spots in their eyes.

APC I1307K mutation

In 1997 scientists identified another mutation on the APC gene, known as I1307K. This mutation is found only in individuals who are of Ashkenazi Jewish descent. It is estimated that about 6% of individuals who are Jewish have this particular mutation. The I1307K mutation itself does not cause an increased risk for colon cancer, but rather makes the APC gene more likely to undergo other genetic changes. These other genetic changes increase a person's risk for developing colon cancer. Genetic testing can be performed on a blood sample to determine if an individual carries the I1307K mutation. A person with this mutation has a 50% chance of passing it on to his or her children.

Cancer risks

Individuals who carry the I1307K mutation have an 18%-30% risk for developing colon cancer over their lifetime. Research is ongoing to determine if individuals with this mutation may also be at risk for developing other types of cancer, such as breast cancer.

Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

HNPCC, also known as Lynch Syndrome, is a condition in which individuals have an increased risk for developing colon cancer, even if there are very few or no polyps present in the colon. It is believed that mutations in one of five cancer susceptibility genes are associated with most cases of HNPCC. These genes are known as hMSH2, hPMS1, MSH6 (all on chromosome 2), hMLH1 (chromosome 1) and hPMS2 (chromosome 7). It is possible that other genes may be found which are also associated with HNPCC. Mutations in these genes are dominantly inherited, and may be able to be detected through genetic testing performed on a patient's blood sample.

Cancer risks

Individuals with an altered HNPCC gene have a much higher risk for developing colon cancer, often at a younger age (less than 50) than people in the general population. Those with an HNPCC mutation are at increased risk for developing other types of cancer, including stomach, urinary tract, bile duct, uterine and ovarian cancer. It is recommended that men and women also be screened closely for these cancers.

Screening and prevention options

It is recommended that all individuals who are at increased risk for developing colon cancer undergo screening for this cancer. Screening for colon cancer consists of two main types of tests. The first test is called a **sigmoidoscopy**. It is performed by inserting a flexible tube, called a sigmoidoscope into the anus to look at the rectum and the lower colon. The doctor can use the scope to see whether polyps may be present, but these growths can not be removed with this test. The second test is known as a **colonoscopy**. While it is very similar to a sigmoidoscopy, it allows a doctor to see the entire colon. Also, with the use of a colonoscope a polyp can be easily removed at the same time a person is undergoing the test. However, because a colonoscopy is a more invasive test, patients have to be sedated. For patients who are at

QUESTIONS TO ASK THE DOCTOR OR A GENETIC COUNSELOR

- What is the likelihood that the cancer in my family is due to a mutation in a cancer susceptibility gene?
- If the cancer in my family is hereditary, what is the chance that I carry a mutation in a cancer susceptibility gene?
- What are the benefits, limitations and risks of undergoing genetic testing?
- What is the cost of genetic testing and how long will it take to obtain results?
- If I undergo genetic testing, will my insurance company pay for testing? If so, will I want to share my results with them?
- What does a positive test result mean for me?
- What does a negative test result mean for me?
- If I test positive for a mutation in a cancer susceptibility gene, what are the best options available for screening and prevention? What research studies may I be eligible to participate in?
- What legislation is in effect to protect me against discrimination by my insurer or employer?

increased risk for developing colon cancer, it is recommended that they undergo this screening at younger ages and more often then individuals in the general population. For example, because cancer can occur at such young ages for individuals with FAP, it is recommended that they have a sigmoidoscopy beginning at age 11.

Finally, men and women with a mutation in a colon cancer susceptibility gene may take certain medications that have been approved for use in individuals with an increased risk for developing colon cancer.

The only way to prevent colon cancer from developing is to remove the colon entirely. If a person with FAP, HNPCC or the I1307K mutation develops colon cancer he/she may choose to have the colon removed. In addition, if an individual is very anxious about developing colon cancer he or she may choose to have the colon removed before cancer develops. There are several different procedures for removing the colon that allow a person to function normally. Women with an HNPCC mutation may also consider prophylactic removal of their ovaries and uterus.

See also Cancer genetics; Familial cancer syndromes.

Resources

ORGANIZATIONS

American Cancer Society. 1599 Clifton Road, NE, Atlanta, GA 30329. (800)ACS-2345. <http://www.cancer.org>.

National Cancer Institute. 31 Center Drive, MSC 2580 Bethesda, MD 20892-2580. (800)4-CANCER. <http://www.nci.nih.gov>.

National Society of Genetic Counselors. 233 Canterbury Drive, Wallingford, PA 19086-6617. (610) 872-7608. <http://www.nsgc.og>.

OTHER

Genetic Health. [cited March 27, 2001]. <http://www.geneticheath.com/>.

Johns Hopkins Hereditary Colorectal Cancer Resources. [cited March 23, 2001]. <http://www.hopkins-coloncancer.org/>.

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Gentamicin *see* **Antibiotics**

Germ cell tumors

Definition

Germ cell tumors are tumors that begin in cells that, in a developing fetus, become sperm or egg cells. Because of the way a baby develops in the womb, these kinds of tumors are found in the ovaries and testes, and in other sites along the midline of the body, such as the brain, the center of the chest, and the center back wall of the abdominal cavity. They can also be found in the center parts of the pelvis, cervix, and uterus, in the vagina or prostate, in the oral or nasal cavities, or on the lips. These tumors are usually discovered either during the first few years of life, or shortly after puberty (when an increase in hormone levels may initiate cancer formation).

Description

Germ cell tumors are a diverse group of tumors that all begin in germ cells, the cells in the developing fetus that become sperm or egg cells. Incidence in the United States is 2–3 cases/million live births. They can occur in the ovaries or testes or outside the reproductive organs in many other locations along the middle of the body. Some are very malignant and some are almost always benign; most require surgery, although some kinds are also treated with additional radiation or **chemotherapy**. Some typically appear in infancy, others are more common in adolescents. The treatment and prognosis will depend on the kinds of tissues present in the tumor and on the location.

Germ cell tumors are divided into two types: germinomas, which contain only immature germ cells; and embryonic tumors, which contain some cells that have started to develop into other tissues (as would happen in normal development of a fetus). Embryonic types of tumor commonly include endodermal sinus tumors, embryonal **carcinoma**, choriocarcinoma and teratoma. Gonadoblastoma and polyembryoma are rare types of embryonic germ cell tumors. Many tumors are mixed, containing more than one cell type.

Generally, any kind of germ cell tumor can appear at any germ cell tumor site, although some types are significantly more common at some locations. For example, about 40% of all germ cell tumors are teratomas in the area of the tailbone, which are typically diagnosed in the first month or two of life. Germinomas and endodermal sinus tumors are most common in the ovaries. Embryonal carcinomas are most common in the testes, usually mixed with endodermal sinus tumors or choriocarcinoma.

Demographics

Like other features of this diverse group of tumors, demographics of this cancer vary with the site and type. The peak in incidence of germ cell tumors during the first few years of life is primarily due to the high numbers of teratomas in the tailbone area, which are about 4 times more common in girls than in boys. The second peak, however, in adolescents reflects a significant

number of testicular cancers in teenage and young adult males. Other common childhood germ cell tumors are tumors of the abdomen, vagina and testicles in infants, brain tumors in childhood, and ovarian tumors in early teens. Adult germ cell tumors in adults are usually in the testes or ovaries. Germ cell tumors are found in all populations of the world in approximately equal numbers.

Causes and symptoms

The causes of germ cell tumors are not well understood, although events at puberty—probably increases in certain hormone level—are thought to play a role in tumors of the ovaries and testicles that occur in adolescents or early teens. Some germ cell tumors have a high percentage of certain genetic sequences, thought to be a possible cause of those types of cancers, while some have a high frequency of abnormal chromosome numbers. Some types of germ cell tumors do tend to run in families. Since germ cell tumors are made up of several different types of cancers, there are probably at least several different causes.

The most common symptom of germ cell tumors is a mass along the midline of the body. This mass may be accompanied by abdominal pain or bloating. Other possible symptoms include:

- constipation
- enuresis (involuntary discharge of urine)
- early entry into puberty
- vaginal bleeding
- late onset of menstruation
- menstrual problems
- excessive hair growth
- weakness in legs
- need to urinate often
- shortness of breath, other breathing problems
- diabetes
- hormonal abnormalities
- stunted growth
- headaches or vision problems

Diagnosis

Most germ cell cancers are initially identified by the discovery of lump in the testicles or somewhere else along the midline of the body. When a lump is identified, often the person's physician will arrange for a **biopsy** of the lump. During a biopsy, a small piece of the lump is removed and cut into thin sections. A specialist examines these sections under a microscope, looking for abnormal kinds of cells. How much the biopsied tissue is different from healthy tissue is a good indication of how severe the disease will probably be, and the results of biopsies are used to give tumors a grade that indicates the patient's chances of survival.

Tests that give a doctor pictures of the tumor are also used, such as x rays, computed tomography (CT, or CAT) scans, or ultrasound. X rays can show the doctors where calcium deposits have occurred in normally soft tissues (an indication of disease). Ultrasound and CT scanning give more details with regard to a specific tumor, such as its site of origin, whether it is solid or cystic, and how well defined its borders are. Well-defined borders have a better chance of complete surgical removal.

Another type of useful test which is specific to germ cell tumors is the measurement of several **tumor markers**. Tumor markers are proteins, often identified in blood samples, that are produced by tumor cells. Two main tumor markers are commonly seen to suggest'a germ cell tumor, alpha-fetoprotein (AFP) and β-Human Chorionic Gonadotropin (β-HCG). Germ cell tumors which produce elevated levels of AFP include endodermal sinus tumors and teratoma, although high levels of AFP are also produced by normal infants. β-HCG is usually associated with tumors which contain elements of the choriocarinoma or embryonic carcinoma types of germ cell tumors. These markers are also used as a measure of the success of surgery or other therapies, and to monitor patients for a recurrence of the disease.

Treatment team

As the understanding of cancer grows and new treatment approach are developed, the complexity of cancer treatment also increases. Today, a multi-disciplinary approach to cancer treatment is considered necessary for effective patient care. People involved in the treatment of a germ cell cancer will typically include the referring physician (often a gynecologist or pediatrician), a gynecological oncologist, a pathologist, and a nurse. If **radiation therapy** is pursued, a radiation oncologist, radiation therapist, radiation nurse, radiation physicist, and a dosimetrist will also be involved. Treatment may also include a psychologist, nutritionist, social worker and chaplain.

Clinical staging, treatments, and prognosis

Staging

Staging and grading tumors is a way of predicting the severity of the disease. Tumor grades are based on the types of tissues present in the tumor; stages

indicate the cancer's spread. Separate staging systems exist for both adult and childhood ovarian cancers and adult and childhood testicular cancers. These are developed separately by groups of pediatric and adult oncologists.

OVARIAN CANCERS Pediatric ovarian cancers are usually graded according to the following scheme: Grade 0 contains only mature tissues (tissues which have already become specific kinds of tissues, rather than primitive developing cells. Grade 1 contains mostly mature tissues, with some immature cells present. Grade 2 contains a moderate amount of immature cells, and in Grade 3, numerous immature cells are present.

Adult **ovarian cancer** is usually staged, with Stage I being found only in the ovaries. Stage II in adult ovarian cancer means that the cancer has spread to the uterus or the fallopian tubes, or other structures in the pelvic area. Stage III tumors are those which have spread to the lymph nodes or outer parts of abdominal organs. Stage IV tumors have spread to the interior of abdominal organs such as the liver or the intestines.

TESTICULAR CANCERS Pediatric testicular cancers are typically staged in a manner similar to adult ovarian cancers: Stage I tumors are limited to the testes, with normal postoperative tumor markers. Stage II tumors have spread to the abdominal lymph nodes and have elevated tumor markers; Stage III have greater involvement of the abdominal lymph nodes. Stage IV tumors have spread to other organs such as the lung.

Adult testicular cancers are commonly staged according to a simplified TNM system. Stage T (with several levels described) indicates a tumor that is localized, N means a tumor that has spread to local lymph nodes, and M means a tumor that has spread to distant lymph nodes and organs.

Treatment

The treatment choice in any specific germ cell tumor depends mainly on the type of tumor and the stage at diagnosis, although the age of the patient and whether or not future childbearing is an issue will also influence treatment choices. Treatment of most germ cell tumors involves surgical removal of the tumor. Advanced cancers normally will be followed by chemotherapy. For some tumors, it may not be possible to completely remove the cancerous tissues. In those cancers, "debulking" surgery will be performed in order to reduce the size of the tumor in order for chemotherapy (or radiation) to be most effective.

Chemotherapy can be given through pills taken by mouth, by injections or through IVs. Chemotherapy works by killing cancerous cells, and can kill cancer cells that have traveled away from the initial site. Therefore, in more advanced stages of disease, chemotherapy will sometimes be the primary treatment. Possibly another surgery will be performed after radiation therapy or chemotherapy is finished. This surgery (second-look surgery) allows the doctor to confirm that cancerous tissues have been eradicated.

Chemotherapy usually involves a platinum-based drug such as **cisplatin** in combination with one or two other anti-cancer medications. These drugs are used in combination because, since they each have different side effects, high doses can be given without increasing the risk of a serious drug reaction. Using combinations also decreases the chance that a cancer will develop resistance to any particular drug. Different combinations of drugs are used to treat different types of tumors.

The treatment of some types of germ cell cancers may follow a slightly different pattern. Germinomas are especially sensitive to radiation. This may be the primary treatment mode for those kinds of tumors. Radiation is used to shrink the size of tumors, and even in ovarian cancers usually involves only external irradiation. The only type of germ cell tumor in children in which radiation is regularly used is germinomas occurring in the brain.

When first-line treatments fail, stronger combinations of drugs may be given, or different, sometimes experimental therapies may be tried. These kinds of therapies includes immune system products like interferons that have been shown to destroy cancerous cells and new drugs being developed that decrease blood flow to tumors. Therapies like immunotoxins, which include anti-cancer drugs attached to antibodies specific to tumor cells, and other ways of making drugs more specific for tumor cells, are also being investigated. Many **clinical trials** for germ cell cancers are evaluating a therapy called "peripheral stem cell rescue," in which the patient's red blood cells are removed before high-dose chemotherapy is given, then replaced after the chemotherapy is complete. This decreases the side effects of the medications and improves the patient's chances of successful treatment.

The prognosis for germ cell tumors depends greatly on the type of germ cell tumor involved and the location in which it is found. Generally, about 90% of patients diagnosed with only localized tumors survive, compared to 50–70% of those who are diagnosed with tumors which have already spread. There is wide variation in the cure rates, depending on the tumor types involved. Mature teratomas of the ovaries, which are by far the most common type of ovarian tumor, are almost always

benign, unless mixed with other, more malignant germ cell tumor types. Choriocarcinomas and embryonal carcinomas, on the other hand, are especially malignant, with an average survival time without treatment of only a few months. Since ovarian cancers are the most difficult to catch early, ovarian cancers of types more malignant than the mature teratoma have the worst prognosis among the germ cell tumors. With modern treatment methods, most often including chemotherapy after surgical removal, survival rates have greatly improved. If caught early, most germ cell tumors have good cure rates.

Alternative and complementary therapies

Alternative and complementary therapies are therapies which fall outside the scope of traditional, first-line therapies like surgery, chemotherapy and radiation. Complementary therapies are meant to supplement those traditional therapies with the objective of relieving symptoms. Alternative therapies are nontraditional, unproven attempts to cure the disease.

Common complementary therapies in germ cell disease include aromatherapy, art therapy, massage, meditation, music therapy, prayer, t'ai chi, yoga, and other forms of exercise. These therapies have the objective of reducing anxiety and increasing a patient's feeling of well-being.

Numerous alternative therapies exist in cancer treatment. Laetril, a product of apricot seeds, is probably one of the most well known. Laetril contains a form of cyanide that may be released by tumor enzymes and may act to kill cancerous cells. However, the product is not approved for use in the United States, and the National Cancer Institute sponsored two clinical trials for the drug in the late 1970s and early 1980s, and decided that no further investigation into the drug was necessary. **Vitamins** and other nutritional elements like vitamins A, C, and E, and selenium are thought to act as **antioxidants**. Vitamin E, melatonin, aloe vera, and a compound called beta-1,3-glucan are thought to stimulate the immune system. Natural substances like garlic, ginger, and shark cartilage are also commonly held to shrink tumors, with less defined modes of action. Antineoplastons are believed by some to be another alternative approach to a cancer cure. Antineoplastons are small proteins which may act as molecular messengers and which may be absent from the urine and blood of many cancer patients. Replacing these proteins may have beneficial effects. After some proposed clinical trials were not completed, the National Cancer Institute draws no definitive conclusions about the effectiveness of antineoplaston therapy. Patients should discuss any supplements with their treating physicians.

Coping with cancer treatment

The use of chemotherapy and radiation therapy in addition to surgery has greatly increased the numbers of germ cell tumor patients who survive; but both of these treatments unavoidably result in damage to some healthy tissues and other undesirable side effects. Some of the more common side effects of chemotherapy include:

- hair loss (**alopecia**)
- **fatigue** and weakness
- **nausea and vomiting**
- bed wetting

Hair loss is a very common side effect of many drugs used to treat cancer. Getting a sample of hair before hair loss begins is desirable in case a wig is desired after hair loss begins. The patient's hair color and texture could then be more closely matched. Hair may thin out gradually or it may come out in big clumps. To slow down the rate of hair loss, avoid any unnecessary sources of damage to the hair, like curling, blow-drying, or chemical treatments.

Hair loss is a difficult part of dealing with cancer for all patients past infancy, especially for teenage patients. Children should be given the right to choose their own way of coping and their choices should be supported. Children may choose to remain bald, or may want to choose hats or scarves instead of wigs. Schools may need to be persuaded to allow a child to wear some kind of head covering. It is important to assure the child that loss of hair is a sign that the medication is doing its job, and that hair loss is temporary.

Hair usually begins regrowth within a few months of the end of intensive chemotherapy, although it may begin to thin out again during the course of maintenance drugs. Sometimes hair comes in a different color or texture than the original hair. It may be a good idea to prepare a child for that possibility.

Fatigue and weakness are other common side effects of chemotherapy. Side effects of the chemotherapy medications, along with the natural depletion of the body's resources as it fights off the disease and normal psychological consequences of the disease such as **depression** combine to make fatigue a very significant part of coping with cancer treatment.

The best way to deal with these symptoms is to cut back on activities and allow plenty of time for resting to let the body heal. Patients should avoid as much extra stress as possible, limiting visitors if necessary in order to avoid being overtired. Children should not be forced into the role of invalid. Children must be allowed to pursue normal activities and hobbies as much as possible.

Parents can best manage this by helping to select those activities that the child considers most important, and by providing a backup plan for times when the child does become too fatigued, such as alternate means of mobility (for example, a stroller, wheel chair or other acceptable and safe vehicle). It is also important to make sure that a well-balanced diet is provided.

Nausea and vomiting are also fairly common side effects of many chemotherapy drugs. Radiation to the brain or the GI tract can also cause nause and vomiting. After a few courses of chemotherapy drugs, some patients will become nauseated just from the thought of an upcoming treatment, or from smelling certain odors that act as nausea triggers. Drugs that combat nausea and vomiting can be prescribed, but are often not effective for anticipatory nausea. There are self-help measures that can be tried. If nausea and vomiting are a problem, heavy, regular meals should be avoided in favor of small, frequent snacks made up of light but nourishing foods like soup. Avoiding food smells and other strong odors may help.

Desensitization, hypnosis, guided imagery, and relaxation techniques may be used if nausea and vomiting are severe. These techniques help to identify the causes which trigger the nausea and vomiting, decrease patient anxiety, and distract the patient from thinking about getting sick. In children, activities like playing video games can be offered as very effective means of distraction.

Bedwetting is another common side effect of anticancer drugs, and one which can be especially distressing for older children. A child who experiences this problem should be reassured that the problem is temporary and will go away when the drug treatment is over. Parents can help the child cope by keeping extra linens ready or covering the wet spot with towels kept handy and most of all, by conveying an attitude that wetting the bed is not a big deal. Children should never be punished. It may also help to limit drinks for a couple of hours before bedtime, or to wake the child at regular intervals overnight to use the bathroom.

The biggest problem for those undergoing radiation therapy is the development of dry, sore, ''burned'' skin in the area being treated. Radiation does not hurt during treatment and does not make the person radioactive. Skin in the treatment area will become red, get itchy and sore, and may blister and peel, becoming painful. Patients with fair skin, or those who have undergone previous chemotherapy have a greater risk of more serious reactions. Dry, itchy or sore skin is temporary; but affected skin may be more sensitive to sun exposure for the rest of the patient's lifetime, so a good sunscreen should be used whenever affected skin is exposed to sunlight.

KEY TERMS

Choriocarcinoma—A highly aggressive malignant germ cell tumor made up of tissue derived from the outer membrane which covers the fetus.

Embryonic carcinoma—A highly malignant germ cell tumor made up of tissues derived from the embryo.

Endodermal sinus tumor—A more aggressive germ cell tumor made up of tissue originating in the nutrient sac of the embryo.

Germinoma—A tumor that develops purely from primitive germ cells.

Gonadoblastoma—A rare and almost always benign form of cancer highly associated with abnormal development of reproductive organs.

Polyembryoma—A very rare, aggressive form of germ cell tumor usually found in the ovaries.

Fear and anxiety are major factors in coping with cancer, including cancer treatments. The feelings are completely normal. Some patients find that concentrating on restful, pleasurable activities like hobbies, prayer, or meditation is helpful in decreasing negative emotions. Support groups are another useful tool, since they provide an environment where fears can be freely expressed and understood.

Clinical trials

Nearly a hundred clinical trials testing new treatments for germ cell tumors are ongoing. New approaches being evaluated emphasize new combinations of existing chemotherapy drugs, peripheral stem cell therapies to supplement chemotherapy, alternative therapies like antineoplastons, and new drug delivery approaches such as immunotoxins.

Therapies being evaluated in clinical trials are usually considered experimental and some, like peripheral stem cell rescue, can be very expensive. Most insurance companies do not cover the costs of experimental therapies.

To find an ongoing clinical trial for a specific kind of germ cell tumor, call the National Cancer Institute at 1-800-4-CANCER.

Prevention

Since the causes of germ cell tumors are not well understood, few identified risk factors exist, thus pro-

QUESTIONS TO ASK THE DOCTOR

- Can you explain what kind of cancer I have?
- Is it a benign or aggressive form of germ cell tumor? Can you explain the grade and stage of my cancer? What are the chances that it will come back?
- How was this cancer diagnosed?
- What is my prognosis?
- What treatments are we going to pursue? What happens if these don't work?
- Do you have experience in treating this type of cancer?
- Is there anything I can do to optimize treatment? Are there any particular side effects I should expect?
- Are there complementary therapies that you would recommend? Any other things that would help me cope with the diagnosis or treatment?

viding little information on the possibility of preventing these kinds of cancers. However, there are ways of improving prognosis with regards to germ cell tumors. Ovarian cancers are difficult to catch in early stages; women who get regular gynecological checkups are more likely to have ovarian cancer diagnosed in more treatable stages. Males who have had **testicular cancer** can improve their chances of catching recurrences in early stages by doing regular self-exams.

Special concerns

A special concern in germ cell tumor patients, especially since most patients are children or young adults, is maintaining these patients' ability to bear children. Unfortunately, all of the common treatments can have a negative effect on future fertility. Radiation, especially, destroys fertility and is avoided in children except for germinomas of the brain. Patients whose reproductive organs must be removed suffer major psychological consequences of the loss of childbearing potential and often, as well, suffer from altered feelings of **sexuality**. The treatment team will attempt to choose treatment options that will preserve the patient's childbearing ability to the best of medical capabilities.

See also Ovarian cancer; Testicular cancer; Extragondal germ cell tumors.

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Wendy Wippel, M.S.

Gestational trophoblastic tumors

Definition

A gestational trophoblastic tumor (GTT) is a rare cancer that develops in tissues formed when a sperm fertilizes an egg but does not create a fetus.

Description

Also known as gestational trophoblastic neoplasms (GTN), these highly curable malignancies originate inside the uterus, in cells (trophoblasts) that make up one layer of the placenta. The most common types of GTT are hydatidiform mole (molar pregnancy) and choriocarcinoma. Placental-site trophoblastic tumor is an extremely rare type of GTT. It originates at the place where the placenta was attached to the wall of the uterus.

Hydatidiform mole

A hydatidiform mole forms when sperm and egg cells unite but do not create a fetus. Cells that form the placenta continue to grow until they look like drops of rain or clusters of grapes. Also known as molar pregnancy, a hydatidiform mole does not spread beyond the uterus.

Choriocarcinoma

Characterized by rapid growth and heavy bleeding, this aggressive, invasive tumor is considered a medical emergency and requires immediate medical attention. Although choriocarcinoma usually originates in a hydatidiform mole, it can also develop in tissue that remains in the uterus following a normal delivery, an abortion, or an ectopic pregnancy.

A malignancy of the trophoblastic cells that form the lining of the uterus (epithelium), choriocarcinoma can spread (metastasize) to any part of the body. **Metastasis** begins at an early stage of the disease and usually involves the lungs, vagina, pelvis, brain, and/or liver. Symptoms of lung metastasis include severe shortness of breath (respiratory insufficiency) and coughing up blood. Irregular, abnormal bleeding can indicate that choriocarcinoma has invaded the vagina. The central nervous system (CNS) is rarely affected unless the disease has spread to one or both lungs; a patient whose brain does become involved may experience headaches, seizures, and stroke-like symptoms. More rarely, choriocarcinoma may spread to the kidneys, spleen, and/or gastrointestinal tract.

Demographics

GTTs occur only in women of childbearing age. These tumors are most common:

- before the age of 16
- after the age of 40
- in women who have had them before
- among women who are poor

Accounting for only 1% of all gynecologic malignancies, GTTs are five times more common in Africa and Asia than in Europe and North America. In the United States, hydatidiform mole occurs in only one of every 1,500 to 2,000 pregnancies.

Causes and symptoms

The cause of GTTs is unknown. A woman's chance of developing a second GTT, while still very low, is about twice as great as her risk of developing a first one.

Symptoms of hydatidiform mole

The most common symptoms of hydatidiform mole are vaginal bleeding and severe morning sickness during the first trimester of pregnancy. Other symptoms that suggest a hydatidiform mole include:

- a uterus larger than expected at a particular stage of pregnancy
- a uterus enlarged on only one side
- a fetus not visible on a sonogram
- absence of fetal heart sounds
- passage of clots with the color and consistency of prune juice or of finger-like structures containing fetal blood cells (villi)
- toxemia
- ovarian cysts
- hyperthyroidism

Recurrent bleeding often causes iron deficiency **anemia** in women who have had a hydatidiform mole. Although molar pregnancy is almost always diagnosed during the first trimester, it is often difficult to distinguish this condition from the early stages of a normal pregnancy. A woman should see her doctor if she experiences abnormal bleeding or cannot feel her baby move when she should.

Symptoms of choriocarcinoma

This GTT occurs in 4% of women whose hydatidiform mole was surgically removed or treated with **radiation therapy**. Following term pregnancies or abortion, the incidence of choriocarcinoma is 1 in 40,000.

A doctor should always consider choriocarcinoma when vaginal bleeding persists after a woman has given birth. Other abnormalities commonly associated with choriocarcinoma are unusual and unexplained neurological symptoms in women of childbearing age and lesions that can be seen on a chest **x ray** but do not cause shortness of breath or other symptoms.

Diagnosis

The process of diagnosing GTT usually begins with an internal pelvic examination that allows the doctor to detect lumps or abnormalities in the size or shape of the uterus. **Imaging studies** such as **computed tomography** (CT) scans, **magnetic resonance imaging** (MRI), and ultrasound may be used to locate tumors. Blood and urine tests measure levels of beta human chorionic gonadotropin (HCG). This hormone is normally produced during pregnancy but is abnormally elevated in the blood and urine of a woman with GTT. HCG is a sensitive marker of the presence of GTT before, during, and after treatment.

After diagnosing GTT, the doctor will perform a regular blood test (every week), pelvic exam (every other week), and chest x ray (every four to six weeks) until the level of HCG in the patient's blood has returned to normal. Once the patient's HCG levels have normalized, medical monitoring includes blood tests with decreasing frequency for the next three years.

Treatment team

GTT is typically treated by a treatment team of gynecologists, gynecologic oncologists, and medical oncologists. A patient who has a poor prognosis should be treated at a specialized trophoblastic disease center by a doctor experienced in caring for high-risk GTT patients.

Clinical staging, treatments, and prognosis

A common system used in U.S. cancer centers to describe the extent (stage) of GTT classifies patients into different prognostic groups. These groups include:

- Nonmetastatic disease: Cancer cells have not invaded tissues outside of the uterus. Cancer found in the muscle of the uterus is called invasive mole or choriocarcinoma destruens.
- Metastatic disease, good prognosis: Cancer cells have invaded tissues outside of the uterus but have not spread to the liver or brain; levels of HCG in the blood are low and the last pregnancy was less than four months ago. No **chemotherapy** treatment has been initiated.
- Metastatic disease, poor prognosis: Cancer cells have invaded tissues outside of the uterus, including the liver or brain; levels of HCG in the blood are high and/or the last pregnancy was more than four months ago. Chemotherapy treatment has been given but was not successful.

Treatment options

Because GTT cells respond well to chemotherapy drugs and HCG blood tests are a reliable means of determining whether cancer cells are still present and if therapy should continue, this disease is one of the most curable cancers of the female reproductive system.

Doctors usually treat GTT with surgery to remove the tumor, followed by chemotherapy taken in pill form or administered intravenously to kill any cancer cells still present after surgery. Radiation therapy is sometimes used to treat GTT that has spread to other parts of the body. Radiation used to treat GTT may be provided by:

- machine (external-beam radiation)
- radiation-producing pellets (radioisotopes) inserted into the area of the body where cancer cells have been found

Choice of treatment is determined by the following factors:

- patient's age and general health
- tumor type
- stage of disease
- areas of the body to which GTT has spread
- HCG levels in the patient's blood
- how much time elapsed between conception and start of treatment
- prior pregnancy-related problems
- extent of treatment for prior pregnancy-related problems
- whether the patient wants to become pregnant in the future

HYDATIDIFORM MOLE Hydatidiform mole is 100% curable with surgery. If the patient wants to become pregnant in the future, the doctor performs **dilatation and curettage** (D&C) with suction evacuation. This procedure involves:

- stretching the opening of the uterus (cervix)
- using a small vacuum-like device to remove material from inside the uterus
- gently scraping the walls of the uterus to remove any remaining material. If the patient does not wish to become pregnant in the future, the doctor removes her uterus (hysterectomy).

Following either of these operations, the doctor carefully monitors the level of HCG in the patient's blood. Chemotherapy is initiated when:

- HCG levels continue to rise for a period of two weeks or remain constant for a period of three weeks
- HCG levels become elevated after having fallen to normal value
- analysis of tissue removed during surgery indicates the presence of invasive disease (choriocarcinoma)
- heavy, unexplained bleeding occurs after material has been evacuated from the uterus

PLACENTAL-SITE GTT Hysterectomy is usually performed to remove cancer cells that have developed where the placenta was attached to the wall of the uterus. Although placental-site GTTs do not generally spread to other parts of the body, they do not respond well to chemotherapy and can be fatal.

NONMETASTATIC DISEASE The most common form of GTT, nonmetastatic disease does not spread beyond the uterus, where its cells develop from tissue remaining after treatment for hydatidiform mole, normal delivery, or abortion. Treatment for nonmetastatic disease consists of single-agent chemotherapy. Hysterectomy is sometimes performed if the patient does not want to become pregnant in the future.

METASTATIC DISEASE, GOOD PROGNOSIS This type of GTT originates as nonmetastatic disease but spreads from the uterus to other parts of the body. The likelihood of cure (prognosis) is considered good if:

- less than four months has elapsed since the patient's previous pregnancy
- HCG blood levels are low
- cancer cells have not spread to the liver or brain
- the patient has not previously received chemotherapy

Doctors may treat metastatic disease with good prognosis with chemotherapy alone, hysterectomy followed by chemotherapy, or chemotherapy followed by hysterectomy. These patients must be carefully monitored. Almost all of these cases can be cured, but between 40% and 50% will develop resistance to the first chemotherapy drug used in treatment.

METASTATIC DISEASE, POOR PROGNOSIS The prognosis for metastatic disease is considered poor if:

- more than four months has elapsed since the patient's previous pregnancy
- HCG blood levels are high
- cancer cells have spread to the liver or brain
- previous chemotherapy treatments did not eradicate the patient's disease

Treatment for this type of GTT must be started immediately and should be performed in a specialized medical center or by a doctor experienced in treating this disease. Treatment usually consists of combination chemotherapy but may include surgery and radiation to parts of the body that cancer cells have invaded.

Metastatic GTT is can also be described as low-risk, medium-risk, or high-risk. This classification enables doctors to identify patients who should be treated with the strongest, most effective combination of chemotherapy drugs. Factors used to determine a woman's risk include:

- age
- prior pregnancy experience
- how much time elapsed between conception and start of treatment
- HGC levels in her blood
- the size of her largest tumor
- where and to how many locations the cancer has spread
- whether she has previously been treated with chemotherapy

RECURRENT DISEASE GTT that recurs after a woman has been treated may reappear in the uterus or in another part of her body. One study indicates that GTT recurs in:

- 2.5% of patients treated for nonmetastatic disease
- 3.7% of patients treated for metastatic disease, good prognosis
- 13% of patients treated for metastatic disease, poor prognosis All these recurrences happened within 36 months of the disappearance of symptoms of the initial disease (remission), while 85% occurred within 18 months of remission.

A woman who develops one or more new GTTs after having been treated with chemotherapy is considered to be a high-risk patient and is categorized as having a poor prognosis. She should subsequently be treated with aggressive chemotherapy. If surgery is not successful in eradicating the cancer, treatment with single-agent chemotherapy is usually indicated unless one or more risk factors indicate that she should receive multiple-drug therapy. When recurrent disease spreads to the central nervous system, whole brain radiation and systemic chemotherapy are given at the same time. About half (50% to 60%) of patients receiving this treatment experience sustained remission. Combination chemotherapy may also be used to treat a woman whose recurrent GTT has spread to the brain.

The prognosis is poor for a woman whose recurrent GTT has spread to her liver; in this case radiation does not improve survival and may make chemotherapy less effective. The prognosis is even poorer if both the liver and brain are affected. "Salvage" surgery is sometimes

KEY TERMS

Ectopic pregnancy—An abnormal pregnancy in which the fertilized egg becomes implanted outside the uterus.

Ovarian cyst—A fluid-filled or semi-solid sac that may be painful or malignant.

Placenta—The organ that develops in the uterus during pregnancy and connects the mother's blood supply with the baby.

Remission—Disappearance or lessening of symptoms.

Salvage surgery—An operation used to treat a patient who has not responded to any other therapy.

Systemic—Affecting the whole body.

Toxemia—An abnormal pregnancy-related condition characterized by high blood pressure, swelling and fluid retention, and proteins in the urine.

QUESTIONS TO ASK THE DOCTOR

- What should I do if I am not sure my pregnancy is proceeding normally?
- Why is it important for me to see my doctor as soon as I realize something might be wrong?
- Will GTT affect my ability to have other children?
- Why must I wait so long before becoming pregnant?

used to treat patients whose disease has not responded to any other available form of treatment.

Disease outcomes

Although very rare in North America, GTT is an important disease because of its life-threatening potential and high curability rates with early, specialized treatment. The probability of cure is high even when the disease has spread far from the uterus. About 70% of patients with high-risk disease go into remission, while the cure rates for properly managed molar pregnancy and vigorously treated nonmetastatic GTT are nearly 100%. About 80% of patients with widely metastasized disease are cured when treated with prompt, aggressive chemotherapy sometimes combined with surgery and radiation.

Combination chemotherapy achieves results in nearly three out of four patients (74%) who have not responded to other forms of treatment, and more than three out of four high-risk patients (76%) who have not previously been treated with chemotherapy. More than half of patients (57%) whose earlier treatment did not eradicate the disease also achieve good results with combination chemotherapy. The survival rate for patients treated with combination chemotherapy is 84%.

Clinical trials

Researchers throughout the United States are currently investigating the following concerns:

- How effective are certain chemotherapy drugs in treating GTT that has not responded to other therapies or that has recurred after treatment?
- At what dosages do specific chemotherapy drugs become toxic?
- How does the frequency of chemotherapy treatments affect a patient's prognosis?
- What is the relationship between the start of chemotherapy and an immediate drop in a patient's HCG levels?

Prevention

The cause of GTT is not known, but the risk is higher than normal for a woman who belongs to blood group A and whose partner belongs to blood group O.

Special concerns

Medical oncologists emphasize the importance of the following treatment factors:

- Chemotherapy should be started as early in the course of the disease as possible.
- Chemotherapy should be administered every 14 to 21 days until HCG blood levels drop to normal.
- High-risk patients should be treated with combination chemotherapy regardless of the stage of their disease.
- Monthly blood tests should be continued for one year after HCG levels drop to normal.
- A woman who has been treated for GTT should wait at least a year before becoming pregnant and see her doctor as soon as she becomes or thinks she might be pregnant.

See also Pregnancy and cancer.

Resources

ORGANIZATIONS

American College of Obstetricians and Gynecologists. 409 12th St. SW, PO Box 96920, Washington, DC 20090-6920. (202) 863-2518. <http://www.acog.org>.

National Cancer Institute. 31 Center Dr., MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

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Maureen Haggerty

Giant cell tumors

Definition

Giant cell tumor generally refers to a bone tumor and is typically found in the end of arm and leg bones.

Description

Giant cell tumor of the bone is also referred to as an osteoclastoma as it contains a large number of giant cells resembling a type of bone cells called osteoclasts. Half of all giant cell tumors occurs in the knee, at the lower end of femur (thigh bone) or upper tibia (one of the bones of the lower leg). The tumor is usually located eccentrically and often causes expansion of the bone end. The tumor destroys the bony structure and thus could lead to fractures, even in the absence of stress. Other giant cell tumors can occur in virtually any other bone, including the sacrum, pelvis, and small bones of hands and feet. The growth of this tumor is variable and unpredictable. It is considered to be benign, but can recur following surgical removal. It can also have pulmonary metastases that are mostly curable. Some of the giant cell tumors may change into malignant **sarcomas**, especially when they recur after high-dose radiation treatment.

Giant cell tumor of tendon sheath

Giant cell tumor of tendon sheath is also referred to a localized nodular tenosynovitis. It usually occurs as single, painless mass that grows slowly. It is mainly found in the wrist and fingers. These are benign growths that can be easily excised (surgically removed). This type is not discussed further in this entry.

Demographics

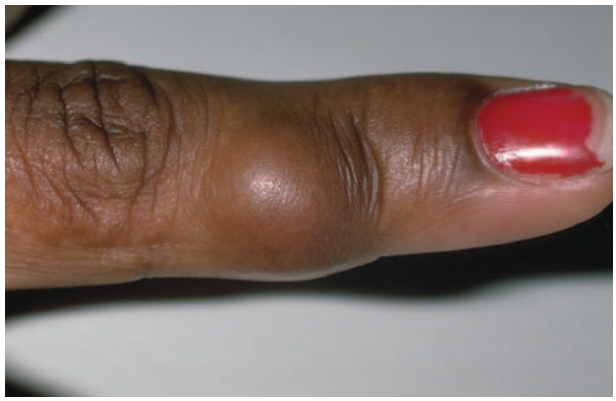
Giant cell tumor of bone is mostly seen in adults between the ages of 20 and 40 years. It is slightly more common among women than men and is seen in Asians more than other ethnic groups. It is very uncommon in children.

Causes and symptoms

The cause of giant cell tumors of bone is unknown.

The following symptoms may be seen in patients with giant cell tumors:

- Pain: As this tumors mainly occurs in the joints, arthritic pain is usually the first symptom.
- Swelling: Giant cell tumor causes enlargement of the bone and, as it grows, the patient may find a swelling at the site of the tumor.



Giant cell tumor of a tendon in a woman's finger. *(Custom Medical Stock Photo. Reproduced by permission.)*

- Fracture: Giant cell tumors destroy the surrounding bone and, unlike other bone cancers, fractures are common as the tumor grows. Initially the patient may have a sore or painful joint and the fracture could make it suddenly, severely painful.

Diagnosis

Typically the patient with giant cell tumor will go to the doctor because of pain. The doctor will perform routine physical tests and test the affected area for tenderness, swelling, warmth, redness, and mobility. An **x ray** of the affected area will be obtained. Certain other imaging tests could be done, including **magnetic resonance imaging** (MRI) and computed tomography (CT scan) to see extent of growth. CT scan of the chest will also be done to test for **metastasis** to the lungs. An isotope scan may be also done to test for extent of damage. These techniques are noninvasive and can be performed within a day. A surgical **biopsy** is always done either before or during surgical removal of the tumor. The biopsy determines whether the tumor is malignant and identifies the stage of the tumor. This may done under either local or general anesthesia, depending upon the location of the tumor and the condition and age of the patient.

Treatment team

The treatment team will consist primarily of radiation oncologist, orthopedic oncologist, and oncology nurse. Following surgical removal of the tumor, recovery may be aided by physical therapists.

Clinical staging, treatments, and prognosis

As of 2001 no satisfactory method for grading the tumor into either benign or malignant was available. Most giant cell tumors are initially classified as benign

KEY TERMS

Computed tomography—Commonly known as CT or CAT scan. It uses a rotating beam of x ray to get internal images of the body from different angles. During this test a harmless dye may be injected to increase contrast between normal and abnormal tissues.

Curettage—Surgical method in which a tumor is scraped away from the healthy tissue.

Magnetic resonance imaging—Also referred to as MRI. A procedure using a powerful magnetic field and radio waves to produce images of internal organs. MRI images can be used to look at soft tissues like muscle and fat.

Sarcoma—Uncommon, malignant tumors that begin in bones, or soft tissues such as muscle or fat.

QUESTIONS TO ASK THE DOCTOR

- What kind of surgery will need to be done for removal of the tumor?
- What will be the limitations after the removal of the tumor?
- Did you find any metastasis in the lungs?
- Is curettage instead of resection a possibility?

(grade 0). The tumor may progress in three stages. Stage 1, or latent stage, consists of a very slow growing tumor. It is well demarcated and there is little destruction of the outer surface of the bone. Stage 2, or the active stage, is the most commonly found stage. In this stage the tumor grows more steadily and the cortex (or outer layer of the bone) is lost. Stage 3 is the aggressive stage and accounts for about 20% of all giant cell tumors. In this stage the tumor grows rapidly and extends beyond the bone into the soft tissue. This stage is also associated more frequently with fractures.

Treatment of giant cell tumors is mainly surgical. Most stage 1 and 2 and some stage 3 tumors are treated by aggressive curettage, and the bone may be treated chemically and filled with cement. In some stage 2 and most stage 3 lesions the affected section of the bone may have to be removed (en bloc resection). In very rare cases the tumor may be so expanded that **amputation** may be necessary. Radiation is used to treat giant cell tumors in a location difficult to treat surgically. **Chemotherapy** has not been shown to be effective against giant cell tumors.

Prognosis following resection is excellent, with less than 5% chance of recurrence. When the tumor is removed by curettage followed by aggressive chemical treatment, there is a 5-10% chance of local recurrence. When the tumors recur locally it is usually within three years of surgical removal and the patient needs to be monitored closely during this time. A small percentage of giant cell tumors can metastasize to the lungs. The metastases can be removed surgically and most can be cured.

When a rare case of malignant sarcoma develops from a giant cell tumor, it is treated aggressively by surgery. In these cases, prognosis is poor and long-term survival rate is as low as 20-30%.

Alternative and complementary therapies

There are no alternative or complementary therapies available for giant cell tumors.

Coping with cancer treatment

As the treatment for giant cell tumors is mainly surgical, physical therapy with strengthening exercises to restore range of motion is extremely important. If amputation is required resulting psychological effects will also have to be addressed, especially as this disease occurs in adults who are physically and sexually active.

Clinical trials

As of 2001 there were no ongoing **clinical trials** by any major agencies specifically for treatment of giant cell tumors.

Prevention

As the cause of giant cell tumors is not known, there is no known method for prevention. When adults in the age group of 20-40 years notice pain and swelling in the joints, prompt radiological evaluation could identify giant cell tumors in early stages and lead to a complete cure.

Special concerns

Whenever a giant cell tumor is suspected, a chest CT scan should also be performed to check for metastasis to the lungs. During pregnancy the tumor can grow more rapidly, in which case it may be better to wait to perform surgery until the baby can be safely delivered by induction. If a patient with giant cell tumor suffers a fracture at the affected area, it may be best to wait until the fracture is healed before performing the surgery.

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ORGANIZATIONS

The American Academy of Orthopaedic Surgeons. 6300 N. River Road, Suite 200, Rosemont, IL 60018. (847) 823–8125. <http://www.aaos.org>.

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Gliomas *see* **Brain/Central nervous system tumors**

Glutamine

Definition

Glutamine is an amino acid that is used as a nutritional supplement in the treatment of a variety of diseases, including cancer.

Purpose

Glutamine is the most abundant free amino acid in the human body and, in addition to its role as a component of protein, serves a variety of functions in the body. It is a non-essential amino acid because it is made by body cells. In addition most dietary protein contains ample amounts of glutamine and healthy people usually obtain all the additional glutamine that they need in their diet.

Cancer and other diseases and injuries induce a state of physiologic stress that is characterized by glutamine deficiency. This deficiency is aggravated by **chemotherapy** and **radiation therapy** used to treat cancer. Therefore, glutamine is sometimes described as a conditionally essential amino acid that needs to be supplemented when the body is stressed.

Cancer-related glutamine deficiency can reduce the tolerance of normal tissues to cancer treatment, necessitating reduced doses and possibly diminishing the effects of treatment. Glutamine supplementation may help protect normal tissues from chemotherapy and radiation while sensitizing tumor cells to these agents.

Increasingly in the early 2000s, glutamine is considered an important component of both oral and parenteral (intravenous) nutrition (PN) therapy during high-dose chemotherapy and radiation treatment. It also is used as a nutritional supplement for bone marrow transplant (BMT) patients, particularly those with leukemia or **lymphoma** whose bone marrow has been destroyed with high-dose chemotherapy.

Glutamine supplementation appears to do the following:

- improve nitrogen retention
- decrease the incidence of infection
- decrease the length of hospitalization, saving thousands of dollars

Glutamine supplementation also appears to reduce the incidence of gastrointestinal, nervous system, and heart complications arising from cancer therapy. Oral glutamine may reduce **diarrhea** and the duration and severity of other gastrointestinal side effects of chemotherapy. In particular it appears to help prevent the intestinal toxicity of the cancer drug **fluorouracil**. Glutamine may reduce the incidence and severity of **mucositis**, a common, painful inflammation of the membranes of the oral cavity that can result from chemotherapy. Rinsing with a glutamine-containing mouthwash can help reduce mouth sores from radiation and chemotherapy treatments. Glutamine also appears to reduce the need for antifungal agents during chemotherapy.

Description

Glutamine (Gln) or L-glutamine is available by prescription as a powder called NutreStore. It is taken as an oral suspension for treating short bowel syndrome. It also is available in nutritional formulas and as an individual nutritional supplement. As an intravenous supplement it may be supplied in the form of alanyl-glutamine dipeptide or glycyl-glutamine dipeptide.

Metabolic effects

There is much speculation about why glutamine appears to be a beneficial adjunct for cancer treatment. Glutamine is required for numerous metabolic processes, including the following:

- Regulation of cell growth and function.
- Synthesis of proteins and nucleic acids (DNA and RNA).
- Movement of nitrogen in the body. Glutamine is the body's primary means of transferring ammonia in a nontoxic form.
- Gluconeogenesis—the formation of glucose from protein and fat.

- Maintenance of acid-base equilibrium in the body.
- As a major fuel for intestinal mucosal cells.
- Improved kidney cell function.

Tumors cause major disruptions in nitrogen and glutamine metabolism. The high rate of protein synthesis in rapidly growing tumors requires a continuous supply of amino acids. Tumors are referred to as nitrogen traps because they actively compete with normal tissues for nitrogen-containing compounds such as glutamine. Tumors also are referred to as glutamine traps because glutamine moves from normal tissues to tumors. Some evidence suggests that glutamine supplementation may diminish tumor growth, in part by improving overall protein metabolism.

Cancer cells generally move glutamine across their cell membranes at a faster rate than normal cells. Glutaminase—the enzyme that breaks down glutamine—has increased activity in cancerous cells, and there is evidence that glutaminase activity correlates with the proliferation of malignant cells.

Immunological effects

Glutamine and arginine may be referred to as immunonutrients because of their important roles in the functioning of the immune system that protects the body from foreign entities, including cancer cells. Glutamine helps to regulate the immune system and is a major fuel for lymphocytes (a type of white blood cell) and other immune system cells. In cancer patients undergoing chemotherapy and total body irradiation, glutamine has been shown to boost the immune system by increasing the levels of circulating lymphocytes and other cells of the immune system.

In patients undergoing chemotherapy with radioactive drugs for advanced **esophageal cancer**, oral glutamine supplementation helped to protect immune system function by causing lymphocytes to divide and multiply. Glutamine supplementation also reduced the permeability of the gastrointestinal tract in these patients.

Antioxidative effects

Glutamine appears to be the rate-limiting factor for the production of liver and intestinal glutathione (GSH), a chemical that protects cells against the damaging effects of oxidation. As cancer cells deplete the glutamine in normal cells, the levels of GSH drop. It has been suggested that PN without added glutamine may itself decrease GSH levels and increase oxidative damage. By increasing GSH levels, oral glutamine supplementation also may increase the selectivity of anticancer drugs by protecting normal cells from oxidative damage caused by the drugs. Glutamine supplementation also appears to protect normal cells from radiation-induced oxidative damage. Since GSH depletion reduces the activity of natural killer cells (immune system cells that destroy cancer cells) glutamine supplementation may increase GSH levels and restore natural-killer-cell activity. Some evidence suggests that this may diminish tumor growth.

Effectiveness

As of 2005, glutamine supplementation during cancer therapy and bone marrow or stem cell transplantation remains under investigation. Although some studies have demonstrated specific benefits in at least some types of cancer, numerous animal and human studies have shown no clear benefit or any effect on tumor response or on the side effects of chemotherapy. However, one study suggested that glutamine supplementation could increase the likelihood of long-term survival in patients with cancers of the blood.

Other studies have found that glutamine supplementation in cancer patients receiving high-dose chemotherapy and BMT decreases the incidence and/or severity of the following:

- chemotherapy-associated mucositis
- diarrhea associated with **irinotecan**, a drug used to treat colon and rectal cancers
- nervous system damage caused by the anticancer drug paclitaxel
- cardiac toxicity caused by the drug anthracycline

Combination supplements

Cancer-related cachexia (severe malnutrition, weakness, and muscle-wasting) is caused by the increased breakdown of proteins and reduced protein synthesis in patients with advanced cancer. One study demonstrated that supplementation with specific nutrients, including a combination of glutamine, beta-hydroxy-beta-methylbutyrate (HMB), and arginine, could reverse these processes. Patients with stage IV cancer who received this combination gained significant fat-free body mass in four weeks and continuing over a period of 24 weeks, as compared to control patients who lost body mass.

Case studies have reported that the administration of glutamine orally and intravenously, in combination with oral vitamin E, decreases the signs and symptoms of hepatic veno-occlusive disease. This is an often-fatal type of liver failure that occurs in patients treated with high-dose chemotherapy in preparation for BMT.

KEY TERMS

Arginine—An essential amino acid derived from dietary protein; sometimes used in combination with glutamine to boost the immune system.

Beta-hydroxy-beta-methylbutyrate, HMB—A nutritional supplement used to buildup muscles and to treat muscle-wasting caused by disease.

Bone marrow transplant, BMT—The destruction of bone marrow by high-dose chemotherapy or radiation and its replacement with healthy bone marrow taken from the patient prior to chemotherapy or from a donor.

Cachexia—Severe malnutrition, weakness, and muscle-wasting caused by disease.

Gluconeogenesis—The formation of glucose from non-carbohydrates such as protein or fat.

Glutaminase—The enzyme that breaks down glutamine; high glutaminase activity may be correlated with the proliferation of cancer cells.

Glutathione (GSH)—A three-amino-acid tripeptide that reduces harmful oxygen radicals and activates some proteins, including natural killer cells.

Hepatic veno-occlusive disease—Liver failure caused by chemotherapy that may benefit from glutamine supplementation.

Lymphocyte—A white blood cell of the immune system, making up 25–33% of all adult white blood cells.

Mucositis—A common, painful inflammation of the membranes of the mouth caused by chemotherapy.

Natural killer cell—A type of lymphocyte that kills cancer cells and certain microorganisms.

Parenteral nutrition (PN)—Intravenous feeding.

Short bowel syndrome—A condition that occurs after a large segment of the small intestine has been removed; it is treated with glutamine.

Tryptophan—An essential amino acid that is sometimes used in combination with glutamine supplementation.

Recommended dosage

Glutamine supplementation generally is started three to five days before chemotherapy. The glutamine dosage used to treat short bowel syndrome is 5 g, six times per day for up to 16 weeks. It is taken with food, every two to three hours while awake. Nutritional guidelines for cancer patients generally recommend 2–4 g of glutamine per day to protect against radiation-induced **enteritis** (intestinal inflammation).

Dosages used in clinical studies of glutamine supplementation in cancer patients vary:

- 18–30 g per day, orally
- 10 g three times per day, orally
- 0.57 g per kg (2.2 lb.) of body weight per day
- 50 g per day of dipeptide glycyl-glutamine, in-travenously
- 0.4 g per kg (2.2 lb.) of body weight per day of dipeptide glycyl-glutamine, intravenously
- 14 g of glutamine per day in combination with arginine and HMB for up to 24 weeks

Precautions

Glutamine, taken orally or by injection, appears to be safe; however, precautions include the following:

- Excess amino acids may be excreted in the urine without being absorbed by the body.
- Excess amino acids can harm the kidneys.
- Glutamine, like any drug, can potentially cause an allergic reaction.
- It is not known whether glutamine supplementation is safe during pregnancy or while breastfeeding.
- Elderly patients may be more sensitive to glutamine supplementation, requiring lower doses.
- Glutamine can worsen liver disease.

Since glutamine is essential for the growth of both healthy and cancerous cells, it is theoretically possible that glutamine could fuel tumor cells, leading to more rapid growth. However, there is no evidence to suggest this, nor is there evidence that glutamine supplementation adversely affects treatment or clinical outcomes.

Side effects

Glutamine supplementation in cancer patients does not appear to cause side effects or adversely affect quality of life.

Interactions

Glutamine supplementation is not known to negatively interact with other medications.

Margaret Alic, Ph.D.

GM-CSF *see* **Sargramostim**

Gonadal dysfunction *see* **Fertility issues**

Goserelin acetate

Definition

Goserelin acetate is a synthetic (man-made) hormone that acts similarly to the naturally occurring gonadotropin-releasing hormone (GnRH). It is available in the United States under the tradename Zoladex.

Purpose

Goserelin acetate is used primarily to counter the symptoms of late-stage **prostate cancer** in men or is offered as an alternative to treat prostate cancer when surgery to remove the testes or estrogen therapy is not an option or is unacceptable for the patient. Goserelin is also given as combination therapy with the drug flutamide to manage prostate cancer that is locally confined and not widespread. It is often used to ease the pain and discomfort of women suffering from endometrosis and to relieve symptoms in women with advanced **breast cancer**.

Description

Goserelin acetate is a man-made protein that mimics many of the actions of gonadotropin-releasing hormone (GnRH). In men, this results in decreased blood levels of the male hormone **testosterone**. In women, it decreases blood levels of the female hormone estrogen.

Recommended dosage

Goserelin acetate is given in the form of an implant containing 3.6 mg of the medication. This implant is placed just under the skin of the upper abdominal wall. The drug lasts for 28 days, after which a new implant has to be placed. Goserelin is also available in a dose of 10.8 mg, in which case the drugs lasts for three months.

Precautions

If a woman becomes pregnant while taking this drug, goserelin acetate may cause birth defects or the loss of the pregnancy. It is not known if goserelin is passed into breast milk; therefore, it is not recommended to breast feed while on this drug.

Goserelin acetate will also interfere with the chemical actions of birth control pills. For this reason, sexually active women who do not wish to become pregnant should use some form of birth control other than birth control pills during treatment with goserelin acetate and for at least 12 weeks after the completion of treatment.

Goserelin acetate will cause sterility in men, at least for the duration of the treatment.

Side effects

In patients of both sexes, common side effects of goserelin acetate include:

- sweating accompanied by feelings of warmth (hot flashes)
- a decrease in sex drive
- depression or other mood changes
- headache
- tumor flare, which is exhibited as **bone pain** (this is due to a temporary initial increase in testosterone/estrogen before its production is finally decreased)

Other common side effects in men include:

- impotence (erectile dysfunction)
- sterility
- breast enlargement

Other common side effects in women include:

- light, irregular, vaginal bleeding
- no menstrual period
- vaginal dryness and/or itching
- emotional instability
- depression
- change in breast size
- an increase in facial or body hair
- deepening of the voice

Less common side effects, in patients of either sex, include:

- nausea and vomiting
- insomnia
- weight gain
- swollen feet or lower legs
- acne or other skin rashes
- abdominal pain
- increased appetite

A doctor should be consulted immediately if the patient experiences any of the above symptoms.

Interactions

There are no known interactions of goserelin acetate with any food or beverage.

Patients taking goserelin acetate should consult their physician before taking any other prescription, over-the-counter, or herbal medication. Patients taking any other

KEY TERMS

Endometrial tissue—The tissue lining the uterus that is sloughed off during a woman's menstrual period.

Gonadotropin releasing hormone (GnRH)—A hormone produced in the brain that controls the release of other hormones that are responsible for reproductive function.

Prostate gland—A small gland in the male genitals that contributes to the production of seminal fluid.

hormone or steroid-based medications should not take goserelin acetate without first consulting their physician.

See also Endometrial cancer; Ovarian cancer.

Paul A. Johnson, Ed.M.

Graft-vs.-host disease

Description

Graft-vs.-host disease is a response by the immune system that occurs when cells from a blood or bone marrow donor attack those of the recipient. The only transplanted tissues that contain enough immune cells to cause graft-vs.-host disease are the blood and the bone marrow. Blood transfusions are used every day in hospitals for many reasons. Bone marrow transplants are used to replace blood-forming cells and immune cells in cancer patients whose own bone marrow has been destroyed by **radiation therapy** or **chemotherapy**.

Blood transfusion graft-vs.-host disease affects mostly the blood. Blood cells perform three functions: carrying oxygen, fighting infections, and clotting. All of these functions are decreased in a transfusion graft-vs.-host reaction, leading to **anemia** (lack of red blood cells in the blood), reduced resistance to infections, and increased bleeding. The reaction occurs 4–30 days after the transfusion.

The tissues most affected by bone marrow graft-vs.-host disease are the skin, the liver, and the intestines. One of these forms of tissue is affected in nearly half of the patients who receive bone marrow transplants.

Bone marrow graft-vs.-host disease comes in both an acute and a chronic form. The acute form appears within two months of the transplant, while the chronic form usually appears within three months. The acute disease produces a skin rash, liver abnormalities, and **diarrhea** that can be bloody. The skin rash is primarily a patchy thickening of the skin. Chronic disease can produce a similar skin rash, a tightening or an inflammation of the skin, lesions in the mouth, drying of the eyes and mouth, hair loss (alopecia), liver damage, lung damage, and indigestion. The symptoms are similar to an autoimmune disease called scleroderma.

Both forms of graft-vs.-host disease bring with them an increased risk of infections, either because of the process itself or its treatment with cortisone-like drugs and immunosuppressives that inhibit the **immune response**. Patients can die of liver failure, infection, or other severe disturbances of their system.

Causes

Cells from the donor who has an active immune system may be transplanted along with the organ or tissue into the host who has a suppressed immune system. These transplanted cells attack the host's body, causing graft-vs.-host disease. Substances made in the body called cytokines are thought to play a role in the development of this reaction. Cytokines are protein substances made by cells that affect other cells.

Even if the donor and recipient are well matched, graft-vs.-host disease can still occur. There are many different components involved in generating immune reactions, and all people (except identical twins) are different. Testing can often find donors who match all the major components, but there are many minor ones that will always be different. Making a match between a donor and recipient depends upon the urgency of the need for a transplant and the chance that a suitable donor will be found.

Treatments

Both the acute and the chronic diseases are treated with cortisone-like drugs, immunosuppressive agents, or with **antibiotics** and immune chemicals from donated blood (gamma globulin). **Cyclosporine** and prednisone are two immunosuppressive drugs that are often used, and **methotrexate** may enhance efficacy. Another way to prevent graft-vs.-host disease is, before transplantation, rid donor bone marrow of the immune cells (T cells) that would attack the recipient's body. Another possibility to avoid complications in **bone marrow transplantation** is to cleanse the bone marrow of cancer cells and use the patient's own cells to grow more bone marrow. Cancer cells that reside in the bone marrow may be removed, leaving behind only those cells that are needed to grow new blood cells (stem cells). These stem cells from the patient can be grown and returned back to the patient.

For recipients of blood transfusions who are especially likely to have graft-vs.-host reactions, the red blood cells can safely be irradiated (using x rays) to kill all the immune cells. The red blood cells are less sensitive to radiation and are not harmed by this treatment.

New directions in research may help to solve the problem of graft-vs.-host disease. A potential source for new stem cells is the umbilical cord. Cells from this area do not give such strong immune reactions and may be useful for re-establishing cell populations. Another potential is to use genetically engineered cells to correct genetic defects in stem cells within the marrow.

Alternative and complementary therapies

Alternative and complementary therapies range from herbal remedies, vitamin supplements, and special diets to spiritual practices, acupuncture, massage, and similar treatments. When these therapies are used in addition to conventional medicine, they are called complementary therapies. When they are used instead of conventional medicine, they are called alternative therapies.

Complementary or alternative therapies are widely used by people suffering with illness. Good nutrition and activities, such as yoga, meditation, and massage, that reduce stress and promote a positive view of life have no unwanted side effects and appear to be beneficial. Alternative and experimental treatments are normally not covered by insurance.

Special concerns

If graft-vs.-host disease is suspected as a complication to a cancer treatment, a skin punch **biopsy** may be performed to confirm this diagnosis. This is a relatively minor procedure in which the skin is anesthetized in a local area and a small piece is removed for testing in the laboratory.

Infection with one particular virus, called cytomegalovirus (CMV), is so likely a complication of graft-vs.-host disease that some experts recommend treating it in advance, using ganciclovir or valacyclovir.

It is an interesting observation that patients with leukemia who develop graft-vs.-host disease are less likely to have a recurrence of the leukemia that was being treated. This phenomenon is called graft-vs.-leukemia.

Bone marrow transplant patients who do not have a graft-vs.-host reaction gradually return to normal immune function in a year. A graft-vs.-host reaction may prolong the diminished immune capacity indefinitely, requiring supplemental treatment with immunoglobulins (gamma globulin). The grafted cells develop a tolerance to the recipient's body after 6–12 months, and the medications can be gradually withdrawn.

KEY TERMS

Anemia—Too few red blood cells, or too little hemoglobin in them.

Immunoglobulin—Chemicals in the blood that defend against infections.

Immunosuppressive—A chemical that suppresses an immune response.

Lesion—Localized disease or damage.

Scleroderma—Progressive disease of the connective tissue of the skin and internal organs.

Graft-vs.-host disease is not the only complication of blood transfusion or bone marrow transplantation. Host-vs.-graft disease, or rejection, occurs when the recipient's immune system is strong enough to attack the transplant. This is also a common occurrence and may require a repeat transplant with another donor organ. Infections are a constant threat in bone marrow transplant because of the disease being treated, the prior radiation or chemotherapy and the medications used to treat the transplant.

See also Bone marrow transplantation; Transfusion therapy.

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Granisetron *see* **Antiemetics**

Gynecologic cancers

Definition

Gynecologic cancers are malignant tumors within the female reproductive organs.

Description

Gynecologic cancers account for approximately 13% of all cancers that affect women. They are responsible for 10% of the cancer deaths among women. Eaxh year, more than 80,000 woman are diagnosed with a gynecologic cancer and 26,0000 women die from these diseases.

The female reproductive tract is comprised of the ovaries, fallopian tubes, uterus, cervix, vagina, and vulva. Together, these organs allow a woman to become pregnant, protect and nourish an unborn baby, and give birth. An understanding of each organ and its role in reproduction may help the patient to understand her particular gynecologic cancer. There are two ovaries, which are the internal organs dedicated to producing eggs. Released eggs are captured by the fallopian tubes, through which the egg (or fertilized egg) travels to the womb (uterus). The lining of the uterus (endometrium) responds to female hormones, such as estrogen, and becomes thickened to allow for implantation of a fertilized egg. The cervix is the opening of the uterus which opens (dilates) during labor to allow for passage of the baby. The vagina is a short tube that extends from the outer female genitalia (vulva) to the cervix.

Gynecologic cancers are defined not solely by the organ affected but also by the type of cancerous cells in the tumor. The type of cancer depends on the cell types that make up an organ. Adenocarcinomas are cancers that contain primarily cells originating from glands or ducts. Squamous cell carcinomas are tumors that arose from squamous cells, the main cell type found in skin. Sarcomas are cancers that originated from cells of basic connective tissue (mesenchymal cells). Sarcomas are comprised of cells that have become specialized (differentiated) and are named according to the predominant cell type. Endometiroid tumors are those that originated from the endometrium. Clear-cell **carcinoma** is a rare gynecologic tumor that contains cells from the mullerian duct, which gives rise to the uterus, vagina, and fallopian tubes during development.

Because the reproductive organs are interconnected, spread of cancer from one organ to another (direct extension) is not uncommon. Gynecologic cancer carries the name of the organ where the cancer originated (primary cancer site). For example, a tumor restricted to the vagina would be "primary vaginal cancer," whereas one that has extended from the cervix to the vagina would be "primary cervical cancer."

Gynecologic cancers

Cancer type	Occurs in	Tumor types
Endometrial cancer	Uterus	Endometrioid tumors Clear-cell carcinomas Papillary serous Sarcomas Mixed tumors
Fallopian tube cancer	Fallopian tubes, but frequently spreads	Serous carcinomas Mucinous tumors Endometrioid tumors
Cervical cancer	Cervix	Squamous cell carcinomas Adenocarcinomas Clear-cell carcinoma Serous carcinoma Glassy-cell carcinoma
Ovarian cancer	Ovaries	Serous carcinomas Mucinous tumors Endometrioid tumors
Vaginal cancer	Vagina	Squamous cell carcinoma Adenocarcinoma Melanoma Sarcoma
Vulvar cancer	Vulva	Squamous cell carcinomas Melanoma Basal cell carcinoma Paget's disease Adenocarcinomas

Although many causes exist for the different gynecologic cancers, new research in 2003 as part of the Women's Health Initiative, a major study, found that estrogen-progestin therapy (hormone replacement therapy) for postmenopausal women may have increased risk for some gynecologic cancers, though data was still being studied in late 2003. New legislation also was introduced in that year to improve early detection of gynecologic cancers.

Types of cancers

Ovarian cancer is the second most common cancer of the female reproductive organs. It accounts for 30% of all gynecologic cancers and 53% of the deaths in this group. The high death rate associated with ovarian cancer is due to the fact that most women are not diagnosed until the cancer has progressed to an advanced stage. The average age at diagnosis is 63 years. Serous carcinomas are the most common type of ovarian cancer. Other common types of ovarian cancer include mucinous tumors and endometrioid tumors.

Fallopian tube cancers, as primary cancers, are very rare. They frequently spread widely within the abdominal cavity. Although often diagnosed earlier than ovarian cancer, fallopian tube cancer produces similar symptoms and originates from similar cell types as ovarian cancer.

KEY TERMS

Differentiated—A term describing cells that have matured normally and have become specialized, such as muscle cells.

Direct extension—The spread of cancer directly from one organ to a neighboring organ, such as from the cervix to the vagina.

Glassy cell carcinoma—Tumorous cells that have a glass-like appearance

Human papilloma virus (HPV)—A sexually transmitted virus that causes genital warts. It is associated with certain gynecologic cancers.

Mucinous tumors—Adenocarcinomas that produce significant amounts of the complex sugar molecule known as mucin.

Papillary serous carcinoma—A serous carcinoma with papillary (nipple-like) outgrowths.

Primary cancer (or tumor)—The organ in which a cancerous tumor originated.

Serous carcinoma—A carcinoma that produces or contains serum, the liquid portion of blood.

Uterine cancer, also called **endometrial cancer**, is the most common gynecologic cancer and accounts for 46% of the cases. Endometrial cancer primarily affects postmenopausal women, however, 25% of cases are in premenopausal women. There are two types of endometrial cancer: estrogen-dependent and non-estrogen-dependent. Estrogen-dependent cancers are usually comprised of well-differentiated cells and are associated with a good outcome and a long survival time. Non-estrogen-dependent cancers are usually made up of poorly differentiated cells and are invasive and associated with a poor prognosis. Uterine tumors are most frequently endometrioid tumors, usually adenocarcinomas. Clear-cell carcinomas, papillary serous, sarcomas, and mixed tumors also occur.

Cervical cancer is the third most common cancer of the female reproductive tract. It accounts for 17% of the gynecologic cancers. Although cervical cancer can affect any adult woman, there are peaks of occurrence around the ages of 37 years and 62 years. Between 60% and 80% of the cases of cervical cancer are squamous cell carcinomas with the remainder being adenocarcinomas. Clear-cell carcinoma, serous carcinoma, and glassy-cell carcinoma are less frequent cervical cancers. Cervical cancer is very strongly associated with **human papilloma virus**.

Vaginal cancer is rare and accounts for just 3% of the gynecologic cancers. It most often strikes women in their sixties. Greater than 90% of the vaginal cancers are squamous cell carcinomas. Adenocarcinoma, **melanoma**, and sarcoma account for the remaining cases. There is an association between vaginal cancer and human papilloma virus.

Vulvar cancer is rare and accounts for 4% of the gynecologic cancers. It most often strikes women in their sixties. Squamous cell carcinoma is the most common type and melanoma is the second most common type of vulvar cancer. Other types of vulvar cancer include **basal cell carcinoma**, Paget's disease, and adenocarcinomas (arising from the Bartholin's, Skene's, or sweat glands). There is an association between vulvar cancer and human papilloma virus.

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American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) ACS-2345. <http://www.cancer.org>.

Cancer Research Institute, National Headquarters. 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

Gynecologic Cancer Foundation. 401 N. Michigan Ave., Chicago, IL 60611. (800) 444-4441 or (312) 644-6610. <http://www.wcn.org/gcf>.

National Institutes of Health. National Cancer Institute. 9000 Rockville Pike, Bethesda, MD 20982. (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

Belinda Rowland, Ph.D.
Teresa G. Odle

H

Hair loss *see* **Alopecia**

Hairy cell leukemia

Definition

Hairy cell leukemia is a disease in which a type of white blood cell called the lymphocyte, present in the blood and bone marrow, becomes malignant and proliferates. It is called hairy cell leukemia because the cells have tiny hair-like projections when viewed under the microscope.

Description

Hairy cell leukemia (HCL) is a rare cancer. It was first described in 1958 as *leukemic reticuloendotheliosis*, erroneously referring to a red blood cell because researchers were unsure of the cell of origin. It became more easily identifiable in the 1970s. There are approximately 600 new cases diagnosed every year in the United States, making up about 2% of the adult cases of leukemia each year.

HCL is found in cells located in the blood. There are three types of cells found in the blood: the red blood cells that carry oxygen to all the parts of the body; the white blood cells that are responsible for fighting infection and protecting the body from diseases; and the platelets that help in the clotting of blood. Hairy cell leukemia affects a type of white blood cell called the lymphocyte. Lymphocytes are made in the bone marrow, spleen, lymph nodes, and other organs. It specifically affects B-lymphocytes, which mature in the bone marrow. However, extremely rare variants of HCL have been discovered developing from T-lymphocytes, which mature in the thymus.

When hairy cell leukemia develops, the white blood cells become abnormal both in the way they appear (by acquiring hairy projections) and in the way they act (by proliferating without the normal control mechanisms). Further, the cells tend to accumulate in the spleen, causing it to become enlarged. The cells may also collect in the bone marrow and prevent it from producing normal blood cells. As a result, there may not be enough normal white blood cells in the blood to fight infection.

Demographics

The median age at which people develop HCL is 52 years. Though it occurs in all ages, HCL more commonly develops in the older population. Men are four times more likely to develop HCL than women. There have been reports of familial aggregation of disease, with higher occurrences in Ashkenazi Jewish men. A potential genetic link is undergoing further investigation.

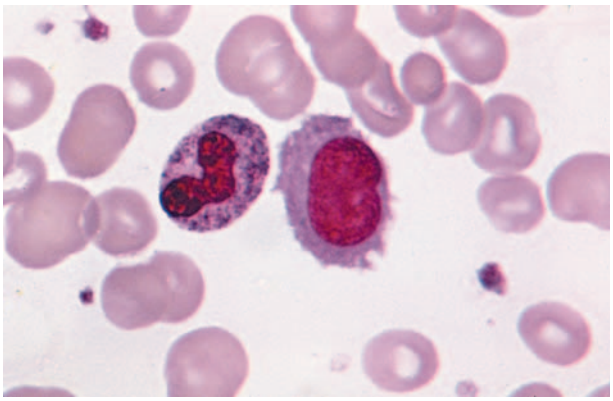
Causes and symptoms

The cause of hairy cell leukemia is not specifically known. However, exposure to radiation is a known cause of leukemia in general. Familial involvement is another theory, suggesting that there is a genetic component associated with this disease.

HCL is a chronic (slowly progressing) disease, and the patients may not show any symptoms for many years. As the disease advances, the patients may suffer from one or more of the following symptoms:

- weakness
- **fatigue**
- recurrent infections
- **fever**
- **anemia**
- bruising
- pain or discomfort in the abdominal area
- weight loss (uncommon)
- night sweats (uncommon)

Pain and discomfort are caused by an enlarged spleen, which results from the accumulation of the



A magnified image of white blood cells with "hairy" projections. *(Photograph by M. Abbey, Photo Researchers, Inc. Reproduced by permission.)*

abnormal hairy cells in the spleen. Blood tests may show abnormal counts of all the different types of cells. This happens because the cancerous cells invade the bone marrow as well and prevent it from producing normal blood cells. Because of the low white cell count in the blood, the patient may have frequent infections. Fever often accompanies the infections. The patient is most susceptible to bacterial infections, but infections of any kind are the major cause of death. The low red cell count may cause anemia, fatigue, and weakness, and the low platelet count may cause the person to bruise and bleed easily.

Diagnosis

When a patient suffers from the above symptoms, the doctor will palpate (examine with fingers) the abdomen and may order scans to see if the spleen is enlarged (splenomegaly). An enlarged spleen is present in 80% of patients. An enlarged liver is less common, but can occur.

If the spleen is enlarged, the doctor may order several blood tests. In these tests, the total numbers of each of the different types of blood cells (CBC) are reported. Sixty to eighty percent of patients suffer from pancytopenia, which is a dramatic reduction in the number of red blood cells, white blood cells, and platelets circulating in the blood.

If the blood tests are abnormal, the doctor may order a **bone marrow aspiration and biopsy**. In order to establish a diagnosis, hairy cells must be present in the bone marrow.

Treatment team

If the patient is seeing a primary care provider, the provider may perform the initial diagnostic tests. However, in order to diagnose and treat HCL comprehensively, the primary care provider will refer the patient to an oncologist (cancer specialist). Radiologists and pathologists will also be involved to read scans and examine tissue samples. Other specialists involved with the treatment of hairy cell leukemia will be nurses and dieticians who are available to explain side effects of treatment and offer suggestions on eating healthy meals that may help fight the side effects.

Clinical staging, treatments, and prognosis

When physicians perform blood tests, they will determine the level of hemoglobin (the oxygen-transporting molecule of red blood cells). Serum hemoglobin levels and the size of the spleen, which can be measured on exam and by using an **x ray**, are proposed criteria for determining the stage of HCL. The following are the three proposed stages and their criteria:

- Stage I: Hemoglobin greater than 12 g/dL (1 g = approximately 0.02 pint and 1 dL = approximately 0.33 ounce) and spleen less than or equal to 10 cm (3.9 inches).
- Stage II: Hemoglobin between 8.5 and 12 g/dL and spleen greater than 10 cm (3.9 inches).
- Stage III: Hemoglobin less than 8.5 g/dL and spleen greater than 10 cm (3.9 inches).

Since there is generally no accepted staging system, another method for evaluating the progression of HCL is to group patients into two categories: untreated HCL and progressive HCL, in which hairy cells are present after therapy has been administered.

Some people with hairy cell leukemia have very few or no symptoms at all, and it is reasonable to expect that 10% of patients may not need any treatment. However, if the patient is symptomatic and needs intervention, HCL is especially responsive to treatment.

There are three main courses of treatment: **chemotherapy**, **splenectomy** (surgical removal of the spleen), and immunotherapy. Once a patient meets treatment criteria, purine analogues, particularly the drugs, **pentostatin** and **cladribine**, are the first-line therapy. Pentostatin is administered at 5mg/m^2 for two days every other week until total remission is achieved. Patients may experience side effects such as fever, nausea and vomiting, photosensitivity, and keratoconjuctivitis. However, follow-up studies estimate a relapse-free survival rate at 76%. Cladribine (2-CdA) taken at 0.1mg/kg/day for seven days also has an impressive response. Eighty-six percent of patients experience complete remission after treatment, while 16% experience partial remission. Fever is the principal side effect of 2-CdA.

Biological therapy (also called immunologic therapy or immunotherapy), where the body's own immune

cells are used to fight cancer, is also being investigated in **clinical trials** for hairy cell leukemia. A substance called interferon that is produced by the white blood cells of the body was the first systemic treatment that showed consistent results in fighting HCL. The FDA approved interferon-alpha (INF-alpha) to fight HCL. The mechanism by which INF-alpha works is not clearly understood. However, it is known that interferon stimulates the body's natural killer cells that are suppressed during HCL. The standard dosage is 2 MU/m^2 three times a week for 12 months. Side effects include fever, myalgia, malaise, rashes, and gastrointestinal complaints.

If the spleen is enlarged, it may be removed in a surgical procedure known as splenectomy. This usually causes a remission of the disease. However, 50% of patients who undergo splenectomy require some type of systemic treatment such as chemotherapy or immunotherapy. Splenectomy is not the most widely used course of treatment as it was many years ago. Although the spleen is not an indispensable organ, it is responsible for helping the body fight infection. Therefore, other therapies are preferred in order to salvage the spleen and its functions.

Most patients have excellent prognosis and can expect to live 10 years or longer. The disease may remain silent for years with treatment. Continual follow-up is necessary to monitor the patient for relapse and determine true cure rates.

Alternative and complementary therapies

Many individuals choose to supplement traditional therapy with complementary methods. Often, these methods improve the tolerance of side effects and symptoms as well as enrich the quality of life. The American Cancer Society recommends that patients talk to their doctors to ensure that the methods they are using are safely supplementing traditional therapy. Some complementary treatments include the following:

- yoga
- meditation
- religious practices and prayer
- music therapy
- art therapy
- massage therapy
- aromatherapy

Coping with cancer treatment

The treatment and the disease interfere with the patient's ability to produce red blood cells, white blood cells, and platelets, causing the patient to be vulnerable to anemia and life-threatening infection and bleeding. Transfusions can be given to patients in order to increase the number of red blood cells and platelets in the blood. In addition, colony-stimulating factors are being studied. These increase the number of the patient's own white blood cells.

Nausea and vomiting can result from chemotherapy and are often controlled by prescription drugs called **antiemetics**. Patients can also curb nausea and vomiting by eating slowly and avoiding large meals. Drinking water an hour before meals and staying away from foods that are sweet or fried is also helpful. Many times, chemotherapy is handled better if the patient is eating well.

KEY TERMS

Anemia—A condition in which there is low iron in the blood due to a deficiency of red blood cells.

Bone marrow—The spongy tissue inside the large bones in the body that is responsible for making the red blood cells, white blood cells, and platelets.

Bone marrow aspiration and biopsy—A procedure in which a needle is inserted into the large bones of the hip or spine and a small piece of marrow is removed for microscopic examination.

Immunotherapy—A mode of cancer treatment in which the immune system is stimulated to fight the cancer.

Keratoconjunctivitis—Inflammation of the conjunctiva and cornea of the eye.

Leukemia—A disease in which the cells that constitute the blood become cancerous or abnormal.

Lymph nodes—Oval-shaped organs that are the size of peas, located throughout the body, and contain clusters of cells called lymphocytes. They filter out and destroy bacteria, foreign particles, and cancerous cells from the blood.

Malignant—Cells that have the ability to invade locally, cause destruction of surrounding tissue, and travel to other sites in the body.

Spleen—An organ that lies next to the stomach. Its function is to remove the worn-out blood cells and foreign materials from the blood stream.

Splenectomy—A surgical procedure that involves the surgical removal of the spleen.

QUESTIONS TO ASK THE DOCTOR

- How long will this course of treatment take?
- How long will the side effects last after treatment ends?
- What kinds of side effects will this course of treatment cause?
- Are there support services available?
- What treatments are currently in clinical trials?
- What treatments will my health care insurance cover?
- What alternative or complementary treatments are safe and effective?
- Why is this type of treatment being used?

Nurses and dieticians can aid patients in choosing healthful foods to incorporate into their diet.

Patients can fight anemia and fatigue by getting plenty of rest and minimizing strenuous activities. A well-balanced diet can also counter anemia and fatigue.

Although physicians will do everything possible to keep a patient's blood count high, there are precautions that can be taken by patients in order to reduce their risk of infection. Patients should regularly wash their hands, especially before and after eating meals and after using the restroom. Patients should avoid individuals who are contagious with colds, the flu, or the chicken pox. It is also helpful if patients do not cut themselves or do anything to expose deeper layers of the skin where bacteria can contaminate and cause infection. Finally, patients should avoid large crowds.

Clinical trials

Clinical trials are being performed to improve the effectiveness of treatment and to minimize the side effects. Patients may choose to volunteer for a clinical trial if they do not respond to standard therapy or if they want to reduce side effects. Clinical trials for the treatment of HCL involving purine analogues were being researched in 2005. Clinical trials are being performed all over the United States, and patients should discuss options with their doctors or contact the Cancer Information Service at (800) 4-CANCER (800-422-6237).

In many cases, insurance companies will not cover procedures that are part of clinical trials. Patients should talk with their doctor and insurance company to determine which procedures are covered.

Prevention

Since the cause for the disease is unknown and there are no specific risk factors, there is no known prevention.

Special concerns

Cancer treatments and their side effects can take a physical and psychological toll on cancer patients and their families. To deal with the psychological impact, there are many different support groups and psychotherapists that can help. Psychiatrists can prescribe medication to help with **depression**. Support groups can encourage and strengthen the psyche by relating to one another through shared experiences and success stories. Relying on faith practices is also beneficial for cancer patients to deal with their condition. Patients should discuss all options with their physician to determine what is available to them.

See also Tumor staging.

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Cancer Research Institute (National Headquarters). 681 Fifth Avenue, New York, N.Y. 10022. (800) 992-2623. <http://www.cancerresearch.org>.

Hairy Cell Leukemia Research Foundation. 2345 County Farm Lane, Schaumburg, IL 60194. (800) 693-6173.

Leukemia Society of America, Inc. National Office, 600 Third Avenue, 4th Floor, New York, NY 10016. (800) 955-4LSA.

National Cancer Institute. 9000 Rockville Pike, Building 31, Room 10A16, Bethesda, Maryland, 20892. (800) 422-6237. <http://wwwicic.nci.nih.gov>.

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Haloperidol *see* **Antiemetics**

KEY TERMS

Dose-limited drug—A drug for which the proper dosage is determined by the reaction of each individual patient to the drug.

Hand-foot syndrome

Description

Hand-foot syndrome (HFS), also called palmar-plantar erythrodysesthesia syndrome (PPES), is a relatively common side effect associated with high dosage **chemotherapy** treatments involving fluorouracil (5-FU) and drugs belonging to the chemical class called anthracyclines.

Anthracyclines have been widely used since the 1960s as dose-limited chemotherapy drugs for a variety of cancers, particularly leukemia, metastatic **breast cancer**, **ovarian cancer**, and colorectal cancer. The most familiar anthracyclines are **capecitabine** (Xeloda), **daunorubicin** (Cerubidine), **doxorubicin** (Adriamycin), **idarubicin** (Idamycin), and **vinorelbine** (Navelbine). Each of these drugs is broken down into 5-FU by chemicals inside the cancer cells.

A dose-limited drug is a drug for which the maximum dose is determined by the reactions of an individual patient. Symptoms of HFS usually indicate that a patient is receiving too much 5-FU or a particular anthracycline. In such a case, the dosage of the drug that is causing HFS is usually decreased until these symptoms either disappear completely or become tolerable to the patient.

The primary symptom of HFS is a tingling sensation and/or numbness of the skin, particularly on the palms of the hands or the soles of the feet. Swelling and redness (erythema) often accompany this symptom. In severe cases, the skin may peel, develop ulcerations or blisters, and cause severe pain. In the most extreme cases, symptoms of HFS may make it difficult, or impossible, for the patient to grasp small objects, walk, or conduct other normal daily activities.

Causes

The symptoms of HFS are believed to be caused by some of the chemicals that 5-FU is broken down into by the natural biochemical processes of the body. Since all anthracycline drugs chemically breakdown into 5-FU, these drugs will all eventually be broken down into the chemicals that can cause the symptoms of HFS. For reasons that are not clear, some patients seem more prone to developing symptoms of HFS than other patients.

Treatments

The symptoms of HFS are usually alleviated by lowering the dosage of the drug that the patient is receiving. In severe cases of HFS, it may be necessary to discontinue the use of the drug that is causing these symptoms. In some, but not all, patients the symptoms of HFS are reduced by treatment with steroid-containing skin creams, such as hydrocortisone.

Alternative and complementary therapies

Treatment of the hands and feet with an aloe vera-containing skin cream may help to alleviate some of the symptoms of HFS. Topical treatment of the skin with dimethyl sulfoxide (DMSO) has also been suggested as an alternative treatment.

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Head and neck cancers

Definition

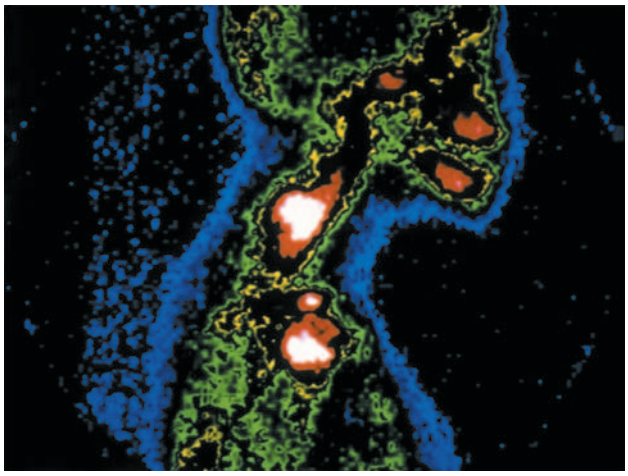
The group of cancers found in the head and neck region, excluding tumors of the eyes and brain.

Description

The tumors associated with head and neck cancers are found in several regions, including the lips, tongue, mouth, nasal passages, pharynx, larynx (voice box), salivary glands, thyroid gland, and parathyroid glands. Many head and neck cancers interfere with the functions of eating and breathing. **Laryngeal cancer** affects speech. Loss of any of these functions is significant. Therefore, early detection and appropriate treatment is of utmost importance.

Roughly 5% of all cancers occur in the head and the neck. The American Cancer Society (ACS) estimates that 56,500 Americans will develop cancer of the head and neck in 2004, and 14,500 will die from the disease.

The most common cancers of the head and neck area are **oral cancers**, **thyroid cancer**, and laryngeal cancer. Half of all head and neck cancers occur in the oral cavity and pharynx, a third are thyroid cancer, and almost 20% are found in the larynx. The American Cancer Society estimates that in 2004 approximately 10,270 new cases of laryngeal cancer will be diagnosed and 3,830 people will die of this disease. New cases of thyroid cancer in 2004 will likely reach over 23,600 and result in 1,460 deaths. Oral cancer is the tenth most common cancer in the United States, reaching nearly 29,000 new cases each year and causing at least 7,300 deaths.



False color scintigram (gamma camera scan) showing metastatic (secondary) cancer affecting the cervical (neck) vertebrae (white area). *(Copyright CNRI, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

The survival rates for head and neck cancers vary from good to poor, depending on the specific cancer. About 54% of the patients diagnosed with oral cancer will survive five years or more after the initial diagnosis. Laryngeal cancer has a five-year survival rate of nearly 65%. Among the different cancers, thyroid cancer has one of the better five-year survival rates, approaching 95%. The poorer survival rates for some head and neck cancers result because the early signs of these cancers are frequently ignored. Hence, when first diagnosed, they are often in an advanced stage and not very amenable to treatment.

Tobacco is regarded as the single greatest risk factor contributing to the occurrence of oral and laryngeal cancer: 75% to 80% of these patients are smokers. Heavy alcohol use has also been included as a risk factor. A combination of tobacco and alcohol use increases the risk for oral cancer by 6 to 15 times more than for users of either substance alone. Exposure to asbestos appears to increase the risk of developing laryngeal cancer. The chance for developing certain types of thyroid cancer is linked to an exposure to radiation. Infection with the Epstein-Barr virus (EBV) is a risk factor for nasopharyngeal cancer.

The risk for both oral cancer and laryngeal cancer seems to increase with age. Most of the cases occur in individuals over 40 years of age, and the average age at diagnosis is 60. While oral cancer strikes men twice as often as it does women, laryngeal cancer is four times more common in men than in women. Both diseases are more common in African Americans than among whites. Thyroid cancer is three times more common in women than in men and is usually diagnosed between the ages of 30 and 50.

Cancers of the head and neck

Cancer types	Cancer occurs in
Hypopharyngeal cancer	Lowest section of the pharynx (region behind mouth)
Laryngeal cancer	Larynx (front of neck, near Adam's apple)
Nasopharyngeal cancer	Behind nose Pharynx
Oral cancer	Lips Lining of lips and cheeks Front two-thirds of tongue Teeth Gums Under tongue
Oropharyngeal cancer	Back one-third of tongue Upper section of pharynx Area around tonsils
Parathyroid cancer	Parathyroid glands (found behind the thyroid gland)
Thyroid cancer	Thyroid gland (found at front of neck, below the Adam's apple)

Types of cancers

There are many types of head and neck cancers. These are classified by where the cancer is found:

- Oral cancers occur in the mouth, or oral cavity, which includes the lips, the lining inside the lips and cheeks, the front two-thirds of the tongue, the teeth, the gums, the floor of the mouth (under the tongue), the roof of the mouth, and the small area behind the wisdom teeth. Symptoms and signs include a mouth sore that does not heal within two weeks, unusual bleeding from the teeth or gums, or a lump in the gums, mouth, or tongue.
- Lip cancers occur on the inside or outside surface of the lips. Signs of this cancer include a lump on the inside of the lip or a sore on the outside, which is usually a form of skin cancer.
- Oropharyngeal cancer is found on the back one-third of the tongue, the upper section of the pharynx, and the area around the tonsils. Symptoms include a lump in the back of the mouth or throat, ear pain, or difficulty swallowing.
- Nasopharyngeal cancer is found in the area behind the nose and the upper section of the pharynx, the area just behind the mouth. Symptoms include difficulty breathing or speaking, pain or ringing in ears, frequent headaches, or trouble hearing.
- Hypopharyngeal cancer is found only in the bottom section of the pharynx. Symptoms include a sore throat that does not subside, difficulty swallowing, a lump in the neck, or ear pain.
- Laryngeal cancer starts in the larynx, which is located in front of the neck, in the region of the Adam's apple. Symptoms include pain when swallowing, a sore throat that does not subside, a change in voice, or ear pain.
- Paranasal sinus cancer and **nasal cancer** develop in the small, hollow spaces in the nose called the sinuses and in the nasal cavity, which is the passageway for air moving to the throat during breathing. Symptoms include frequent sinus infections, nosebleeds, a sore inside the nose that does not heal, or pain in the sinus area.
- Salivary gland tumors form in the salivary glands, which produce saliva to help prevent the mouth from drying out and aids with digestion. They are located under the jaw, in front of the ears, underneath the tongue, and in other regions of the digestive tract. Symptoms include swelling under the chin or around the jawbone, facial numbness, muscles in the face that will not move, or persistent pain in the face, chin, or neck.
- Thyroid cancer is found on the thyroid gland, which is located in the front of neck and secretes hormones that help regulate body temperature and metabolism. Symptoms include a lump on the neck, pain in the neck region, a cough with bleeding, or difficulty swallowing or breathing.
- Parathyroid cancer is found on one or on all four of the small parathyroid glands, which secrete a hormone that controls the level of calcium in the blood. They are located in neck area, with a pair on either side of the thyroid gland. Symptoms include **bone pain**, a lump in the neck, weak muscles, or nausea.

Treatment

Most head and neck cancers are treated initially with surgery and/or radiation therapy; chemotherapy may also be used to shrink tumors, but is more commonly given as palliative treatment to patients whose cancers have not responded to surgical removal or radiotherapy. The most common drugs used in treating head and neck cancers are cisplatin, fluorouracil, bleomycin, and methetrexate.

A newer form of radiotherapy that has proved beneficial to patients with head and neck cancer is intensity-modulated radiation therapy, or IMRT. IMRT allows the radiologist to deliver controlled doses of radiation to cancerous tissues while leaving nearby normal tissues and organs unaffected.

KEY TERMS

Larynx—The voice box or sound-producing organ in the body, located in the upper section of the trachea (windpipe). The movement of the muscles of this organ alters the sounds emitted by the vocal cords.

Palliative care—Care that is given to relieve the symptoms of a disease without curing it.

Pharynx—The space behind the mouth that connects to the trachea and the esophagus (swallowing tube). It serves as a passageway for food and air.

Risk factor—Anything that increases a person's chance of developing a disease.

One of the most difficult aspects of treating head and neck cancer for many years has been the necessity of reconstructive surgery and rehabilitation therapy following removal of the patient's lips, tongue, voice box, or other structures. Recent advances in reconstructive surgery, however, have provided patients with better functioning as well as appearance, thus improving their quality of life as well as length of survival.

See also Alcohol consumption; Cigarettes; Laryngeal nerve palsy.

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Health insurance

Definition

Health insurance is insurance that pays for all or part of a person's health care bills. The types of health insurance are group health plans, individual plans, workers' compensation, and government health plans such as Medicare and Medicaid.

Health insurance can be further classified into fee-for-service (traditional insurance) and managed care. Both group and individual insurance plans can be either fee-for-service or managed care plans.

The following are types of managed care plans:

- Health Maintenance Organization (HMO)
- Preferred Provider Organization (PPO)

Purpose

The purpose of health insurance is to help people cover their health care costs. Health care costs include doctor visits, hospital stays, surgery, procedures, tests, home care, and other treatments and services.

Description

Health insurance is available to groups as well as individuals. Government plans, such as Medicare, are offered to people who meet certain criteria.

Group and individual plans can be further classified as either fee-for-service or managed care. Cancer patients may have specific concerns, such as the freedom to select specialists, that play a factor in choosing a health care plan. Fee-for-service plans traditionally offer greater freedom when choosing a health care professional. Managed care often limits a patient to health care professionals listed by the managed care insurance company.

Group health plans

A group health plan offers health care coverage for employers, student organizations, professional associations, religious organizations, and other groups. Many employers offer group health plans to employees and their dependents as a benefit of working with that particular employer (medical benefits). The employer may pay for part or all of the insurance cost (premium).

When an employee leaves a job he or she may be eligible for continued health insurance as a result of the Consolidated Omnibus Budget Reconciliation Act of 1986 (COBRA). This federal law protects employees and their families in certain situations by allowing them to keep his or her health insurance for a specified amount of time. The individual must, however, pay a premium to keep their insurance plan in effect It is important to note that COBRA only applies under certain conditions, such as job loss, death, divorce, or other life events. The COBRA law usually applies to group health plans offered by companies with more than 20 employees. Some states have laws that require employers to offer continued health care coverage for people who do not qualify for COBRA. Each state's insurance board can provide additional information.

Individual plans

These type of health care plans are sold directly to individuals.

Fee-for-service

Fee-for-service is traditional health insurance in which the insurance company reimburses the doctor, hospital, or other health care provider for all or part of the fees charged. Fee-for-service plans may be offered to groups or individuals. This type of plan gives people the highest level of freedom to choose a doctor, hospital, or other health care provider. A person may be able to receive medical care anywhere in the United States and, often, in the world.

Under this type of insurance a premium is paid and there is usually a yearly deductible, which means benefits do not begin until this deductible is met. After the person has paid the deductible (an amount specified by the terms of the insurance policy) the insurance company pays a portion of covered medical services. For example, the deductible may be $250 so the patient pays the first $250 of yearly covered medical expenses. After that he or she may pay 20% of covered services while the insurance company pays 80%. The exact percentages and deductibles will vary with each policy. The person may have to fill out forms (claims) and send them to the insurance company to have their claims paid.

People who have cancer may be attracted to the freedom of choice that traditional fee-for-service plans offer. However, they will most likely have higher out-of-pocket costs than they would in a managed care plan.

Managed care

Managed care plans are also sold to both groups and individuals. In these plans a person's health care is managed by the insurance company. Approvals are needed for some services, including visits to specialist doctors, medical tests, or surgical procedures. In order for people to receive the highest level of coverage they must obtain services from the doctors, hospitals, labs, imaging centers, and other providers affiliated with their managed care plan.

People with cancer who are considering a managed care plan should check with the plan regarding coverage for services outside of the plan's list of participating providers. For example, if a person wants to travel to a cancer center for treatment, he or she should find out what coverage will be available. In these plans coverage is usually much less if a person receives treatment from doctors and hospitals not affiliated with the plan.

HEALTH MAINTENANCE ORGANIZATION (HMO) An HMO is a type of managed care called a prepaid plan. This type of coverage was designed initially to help keep people healthy by covering the cost of preventive care, such as medical checkups. The patient selects a primary care doctor, such as a family physician, from an HMO list. This doctor coordinates the patient's care and determines if referrals to specialist doctors are needed. People pay a premium, usually every month, and receive their health care services (doctor visits, hospital care, lab work, emergency services, etc.) when they pay a small fee called a copayment. The HMO has arrangements with caregivers and hospitals and the copayment only applies to those caregivers and facilities affiliated with the HMO. This type of coverage offers less freedom than fee-for-service, but out-of-pocket health care costs are generally lower and more predictable. A person's out-of-pocket costs will be much higher if he or she receives care outside of the HMO unless prior approval from the HMO is received.

PREFERRED PROVIDER ORGANIZATION (PPO) A PPO combines the benefits of fee-for-service with the features of an HMO. If patients use health care providers (doctors, hospitals, etc.) who are part of the PPO network, they will receive coverage for most of their bills after a deductible and, perhaps a copayment, is met. Some PPOs require people to choose a primary care physician who will coordinate care and arrange referrals to specialists when needed. Other PPOs allow patients to choose specialists on their own. A PPO may offer lower levels of coverage for care given by doctors and other professionals not affiliated with the PPO. In these cases the patient may have to fill out claim forms to receive coverage.

Government health plans

Medicare and Medicaid are two health plans offered by the U.S. government. They are available to individuals who meet certain age, income, or disability criteria. TRICARE Standard, formerly called CHAMPUS, is the health plan for U.S. military personnel.

MEDICARE Medicare, created in 1965 under Title 18 of the Social Security Act, is available to people who meet certain age and disability criteria. Eligible people include:

- those who are age 65 years and older
- some younger individuals who have disabilities
- those who have end-stage renal disease (permanent kidney failure)

Medicare has two parts: Part A and Part B. Part A is hospital insurance and helps cover the costs of inpatient hospital stays, skilled nursing centers, **home health services**, and **hospice care**. Part B helps cover medical services such as doctors' bills, ambulances, outpatient therapy, and a host of other services, supplies, and equipment that Part A does not cover.

MEDICAID Medicaid, created in 1965 under Title 19 of the Social Security Act, is designed for people receiving federal government aid such as Aid to Families with Dependent Children. This program covers hospitalization, doctors' visits, lab tests, and x rays. Some other services may be partially covered.

TRICARE Eligible military families may enroll in TRICARE Prime, which is an HMO; TRICARE Extra, which offers an expanded choice of providers; or TRICARE Standard, which is the new name for CHAMPUS.

Supplemental insurance

Supplemental insurance covers expenses that are not paid for by a person's health insurance. Cancer insurance is a specific form of supplemental insurance that covers expenses that are not normally covered by health insurance but are specifically related to cancer treatments.

Workers' compensation

Workers' compensation covers health care costs for an injury or illness related to a person's job. Medical conditions that are unrelated to work are not covered under this plan. In some cases an evaluation is done to determine whether or not the medical condition is truly related to a person's employment.

KEY TERMS

Clinical trial—A study to determine the efficacy and safety of a drug or medical procedure. This type of study is often called an experimental or investigational procedure.

Health care provider—A doctor, hospital, lab, or other professional person or facility offering health care services.

Health insurance claim—A bill for health care services that is turned in to the health insurance company for payment.

Special concerns

There are a variety of special concerns that people with cancer have regarding health insurance.

Waiting period

Insurance may not take effect immediately upon signing up for a policy. Sometimes a waiting period exists, during which time premiums are not paid and benefits are not available. Health care services received during this period are not covered.

Preexisting condition

A preexisting condition, such as cancer, is a concern when choosing insurance. If a person received medical advice or treatment for a medical problem within six months of enrolling in new insurance, this condition is called preexisting, and it can be excluded from the new coverage. The six-month time lapse before a person enrolls in a new health insurance policy is called the look-back period. If a person received medical advice, recommendations, prescription drugs, diagnosis, or treatment for a health problem during the look-back period, he or she is considered to have a preexisting condition.

People should check with their state insurance boards to determine preexisting condition rules.

Coverage renewal

Some people with diseases such as cancer worry about group health plans renewing their coverage. As long as the person meets the plan's eligibility requirements and the plan covers similar cases, the coverage must be offered. Coverage cannot be cancelled for health reasons.

Experimental/investigational treatments

Experimental/investigational treatments are often a concern for people with cancer. These treatments may or may not be covered by a person's health insurance. Some states mandate coverage for investigational treatments. People should check with their insurance plans and state insurance boards to determine if coverage is available.

A clinical trial is a type of investigational treatment. Costs involved include patient care costs and research costs. Usual patient care costs that may be covered by insurance are visits to the doctor, stays in the hospital, tests, and other procedures that occur whether a person is part of an experiment or is receiving traditional care. Extra patient care costs that may or may not be covered by insurance are the special tests required as part of the research study.

Health insurance plans have policies regarding coverage for **clinical trials**. People should determine their level of health insurance coverage for clinical trials, and they should learn about the costs associated with a particular study.

In 2000, Medicare began covering certain clinical trials. The trials must meet specific criteria in order to be covered. In eligible trials treatments and services such as tests, procedures, and doctor visits that are normally covered by Medicare are covered. Some items may not be covered including investigational items like the experimental drug itself or items that are used only for data collection in the clinical trial. Patients should check to see if the clinical trial sponsor is providing the **investigational drug** at no charge.

Complementary therapies

Complementary cancer therapies are another coverage consideration. A cancer patient undergoing this type of therapy should check with his or her insurance policy regarding coverage.

Cancer screening coverage

Cancer screening coverage is an important consideration. Forty-four states mandate insurance coverage of screenings for at least one of these cancers: breast, cervical, prostate, and colorectal. **Breast cancer** screening coverage is most commonly mandated. Most mandates refer to screenings that follow the American Cancer Society guidelines. A Women's Health Initiative Observational Study investigated the use of cancer screenings by more than 55,000 women between September 1994 and February 1997. The study found that the type of insurance a woman had was linked with the number of cancer screenings she reported. Women age 65 years and older who had Medicare plus prepaid insurance were more likely to report that they had screenings than those who had Medicare alone.

QUESTIONS TO ASK THE DOCTOR

- What types of insurance do you accept?
- Does your office file claims for patients?
- Will your office get pre-authorization for procedures where it is required?
- Do you have a list of providers for my type of insurance in case a referral is necessary?
- If an experimental procedure is recommended, what costs will be involved?

Health care regulations

The Health Insurance Portability and Accountability Act (HIPAA), passed by the U.S. Congress in 1996, offers people rights and protections regarding their health care plans. Because of HIPAA, there are limits on preexisting condition exclusions, people cannot be discriminated because of health factors, there are special enrollment requirements for people who lose other group plans or have new dependents, small employers are guaranteed group health plan availability, and all group plans have guaranteed renewal if the employer wishes to renew. In summary these rights and protections include:

- Portability. This is the ability for a person to get new health insurance if a change is desired or needed.
- Availability. This refers to whether or not health insurance must be offered to a person and his or her dependents.
- Renewability. This refers to whether or not a person is able to renew his or her health plan.

The Women's Health and Cancer Rights Act of 1998 requires health insurance plans to cover breast reconstruction related to a **mastectomy** if the patient

chooses to have reconstruction and if the health plan covered the mastectomy. The law became effective for different health plans on different dates, with the earliest date of effect being October 21, 1998.

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Rhonda Cloos, R.N.

Hemolytic anemia

Description

Red blood cells (erythrocytes) transport oxygen and carbon dioxide in the bloodstream, maintain a normal acid-base balance, and determine how thick or thin the blood is. Hemolytic anemia refers to the premature, increased destruction of erythrocytes. Hemolysis is the rupture of these erythrocytes with the release of hemoglobin into the plasma, and anemia is a reduced delivery of oxygen to the tissues. Some of the symptoms of hemolytic anemia include nosebleeds, bleeding gums, shortness of breath, **fatigue**, rapid heartbeat, pale skin color or yellow skin color (jaundice), chills, and dark-colored urine.

Causes

Erythrocyte (red blood cell) formation takes place in the red bone marrow in an adult and in the liver, spleen, and bone marrow of the fetus. Their formation requires an adequate supply of iron, cobalt, copper, amino acids, and certain **vitamins**. When the bone marrow loses its ability to compensate for the destruction of the erythrocytes by increasing their production, hemolytic anemia occurs. There are many types of hemolytic anemia, which are classified according to the location of this inability to produce red blood cells. If the problem lies within the red blood cell itself, it is referred to as an intrinsic factor, and if the problem is outside the red blood cell, it is referred to as an extrinsic factor. The overall incidence of hemolytic anemia is approximately 4 per 100,000 people.

Rh factor incompatibility refers to genetically determined substances capable of producing an **immune response** (antigens). This can cause hemolytic anemia not only during pregnancy when the mother is Rh negative and the fetus is Rh positive, but in mismatched blood transfusions as well. There are a number of industrial poisons that produce hemolytic anemia. These include:

- antimalarial agents
- organic solvents (benzene)
- certain chemotherapies
- hypersensitivity to certain antibiotics
- metals (chromium, platinum salts, nickel, lead, copper)
- Pyridium
- arsenic
- intravenous (IV) water (an IV that is not normal or half-normal saline)
- snake bites (if the venom contains hemolytic toxins) These are all factors external to the red blood cell and thus are extrinsic in nature.

One important extrinsic factor in the cause of hemolytic anemia is in the course of widespread cancer, leukemia, **Hodgkin's disease**, acute alcoholism and liver disease. Many of the **chemotherapy** agents (**cisplatin**, **carboplatin** and nonplatinum drugs) utilized in treating various cancers have side effects that cause a suppression of bone marrow activity, which results in severe hemolytic anemia. In essence, an individual is not only anemic as a result of cancer, but this anemia is worsened by the treatment. Since nausea, vomiting, and lack of appetite

KEY TERMS

Erythrocytes—Red blood cells.

Erythropoietin—A glyco-protein hormone secreted by the kidney in the adult and by the liver in the fetus, which acts on stem cells of the bone marrow to stimulate red blood cell production (erythropoiesis).

Hemolysis—The rupture of red blood cells with the release of hemoglobin into the plasma.

Spherocytosis—The presence of small, round erythrocytes that have a smaller surface area than normal and carry less oxygen as a result.

Stem cells—Any precursor cell having the ability to both replicate and differentiate and give rise to other precursors of different blood cell lines.

Thalassemia—A hereditary hemolytic anemia marked by a decreased rate of synthesis of hemoglobin chains.

are also side effects of chemotherapy, it is extremely difficult for the patient to overcome this anemia with diet and supplements. Eventually, severe hemolytic anemia is the end result.

Intrinsic factors would include disorders in the immune response and genetically inherited disorders such as glucose-6-phosphate dehydrogenase deficiency, an essential enzyme. People with this disorder do not display any symptoms until exposed to certain medications or stress. Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) can precipitate this reaction. This disorder is more common among African-American males, with approximately 10% to 14% of the population being affected. Other genetic disorders include sickle cell anemia, thalassemia, and spherocytosis. All of these produce structurally abnormal red blood cells to varying degrees.

Treatments

The treatment depends upon the cause and severity of the anemia. Medicines like **folic acid** and **corticosteroids** may be used to treat the anemia if it is not severe. Severe hemolytic anemia may be very quickly fatal and immediate hospitalization is required for transfusion of washed and packed red blood cells. Severe anemias can aggravate pre-existing heart disease, lung disease and cerebrovascular disease.

Frequently with cancer treatments, a patient may undergo numerous blood transfusions to accomodate for the severe anemia suffered as a result of chemotherapy. Researchers, investigating ways to enhance the quality of life for chemotherapy patients, have primarily looked at controlling pain and loss of appetite (**anorexia**). Recent studies, however, have examined the use of **erythropoietin** (a protein hormone that stimulates red blood cell production) in improving fatigue symptoms and enhancing overall quality of life. Once-weekly therapy with erythropoietin was found to increase hemoglobin levels, decrease transfusion requirements, and improve quality of life in patients with cancer and anemia undergoing chemotherapy.

Alternative and complementary therapies

Since there is no known prevention for hemolytic anemia, there is relatively little that can be done except to be aware of the risk factors and know the potential for genetic disorders within the family. Avoiding exposure to chemicals that precipitate the reaction, eating natural, whole grain foods, avoiding stress, and taking vitamin supplements can be helpful. With cancer patients, yoga and meditation provide a means of enhancing relaxation, reducing stress, and incorporating visualization for healing. Those patients who attend and participate in support groups have an increased quality of life with better outcomes from treatments.

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Hemoptysis

Description

Hemoptysis is the coughing up of blood or bloody sputum from the respiratory tract. The blood can come

from the nose, mouth, throat, airway passages leading from the lungs, or the lungs.

Hemoptysis can range from small quantities of blood-stained sputum to life-threatening amounts of blood. Massive hemoptysis is defined as the spitting up of so much blood that it interferes with the patient's breathing. Generally, this is 200 to 600 or more milliliters of blood coughed up within a 24 hour period. Massive hemoptysis is considered a medical emergency. Up to 75 percent of patients with massive hemoptysis die from asphyxiation (lack of oxygen) caused by too much blood in the airways.

Hemoptysis refers specifically to the spitting up of blood that comes from the respiratory tract. Often when persons spit up blood, they are not spitting up blood from the respiratory tract, but from somewhere else. When the blood comes from somewhere other than the respiratory tract, such as from a bloody nose or from the gastrointestinal tract, this is called pseudohemoptysis. Vomiting up blood from the gastrointestinal tract, called hematemesis, is one type of pseudohemoptysis. It is important to distinguish between true hemoptysis and pseudohemoptysis because they often involve very different parts of the body and the treatments are radically different.

Causes

Hemoptysis is caused by a variety of medical conditions including tuberculosis, bronchitis, bronchiectasis, **pneumonia**, and respiratory tract trauma. It is also caused by many forms of lung and respiratory tract cancers, such as: bronchial **carcinoma**, bronchial **adenoma**, respiratory tract hemangioma, and occasionally by metastatic cancer to the lungs.

Treatments

The goal of treatment for patients with hemoptysis is to stop the bleeding as soon as possible while also treating the cancer or other underlying disorder that is causing the hemoptysis.

Hemoptysis generally will stop spontaneously and no treatment is necessary, apart from reassurance of the patient that this condition will resolve on its own. Therefore, the general treatment for hemoptysis is to keep the patient calm and to ensure complete bed rest.

If the coughing that accompanies the hemoptysis is troublesome or aggravating the condition, cough suppressants may be recommended.

In cases of massive hemoptysis, the placement of a tube in the respiratory tract (intubation) may be necessary to allow for adequate airflow into and out of the respiratory tract. A **bronchoscopy** may be performed, not only to clear the airway of blood, but also to assist in diagnosing the endobronchial cause of the hemoptysis. When large amounts of blood have been lost, the patient may also require intravenous (IV) fluids and/or a blood transfusion.

In the most severe cases of hemoptysis, surgery to remove the cancer that is causing the spitting up of blood may be necessary to relieve the symptoms of hemoptysis. Other treatment modalities include PDT (photodynamic therapy).

KEY TERMS

Bronchial adenoma—A tumor arising in the linings of the bronchi.

Bronchial carcinoma—Cancer arising from the bronchi, the major vessels that convey air to and from the lungs to the mouth and nose.

Hemangioma—A tumor of the blood vessels that is usually present at birth. When these occur on a visible portion of the skin, they are called "birthmarks." When they occur within the respiratory tract, they may lead to hemoptysis.

Sputum—Material ejected from the lungs, bronchi, or trachea, through the mouth.

Alternative and complementary therapies

Inhalation of the fumes of a tea made from the bark of the wild cherry (*Prunus virginiana*) tree has been an herbal remedy for many respiratory tract ailments, including tuberculosis and hemoptysis among the Native Americans for centuries.

Hydrazine sulfate, a naturally occurring monoamine oxidase inhibitor (MAOI), has also been suggested as a treatment for hemoptysis.

Resources

ORGANIZATIONS

The Alliance for Lung Cancer (ALCASE). 1601 Lincoln Avenue, P. O. Box 849, Vancouver, WA 98666. Telephone 1-800-298-2436. Fax 360-735-1305. <http://www.alcase.org>.

American Lung Association (ALA). 1740 Broadway, New York, NY 10019. Telephone 1-212-315-8700. <http://www.lungusa.org>.

Paul A. Johnson, Ed.M.

Heparin

Definition

Heparin is a drug that helps prevent blood clots from forming and belongs to the family of drugs called anticoagulants (blood thinners), although it does not actually thin the blood. It is sold in the United States under the brand names of Calciparine, Liquaemin, Calciparine, Hepalean, and Heparin Leo, and Calcilean in Canada.

Purpose

Heparin is used to decrease the clotting ability of the blood and to help prevent harmful clots from forming in the blood vessels. Heparin will not dissolve blood clots that have already formed, but it may prevent the clots from becoming larger and causing more serious problems. Heparin possesses several antithrombotic mechanisms. It is often used as a treatment for certain blood vessel, heart, and lung conditions and is also used to prevent blood clotting during open-heart surgery, bypass surgery, and dialysis. Heparin is used in low doses to prevent the formation of blood clots in certain patients, especially those who must have certain types of surgery or who must remain in bed for a long time. It is also used for the long-term treatment of thromboembolic disease, a common side effect of cancer.

One of the most common hematological complications is disordered coagulation. Approximately 15% of all cancer patients are affected by thromboembolic disease, which is the second leading cause of death for cancer patients. However, thromboembolic disease may represent only one of many complications in end-stage patients. Thromboembolic disease includes superficial and deep venous thrombosis, pulmonary emboli, thrombosis of venous access devices, arterial thrombosis, and embolism. The cancer itself or cancer treatments may induce coagulation. For example, **chemotherapy** can increase the risk of thromboembolic disease. An increased risk for arterial thrombosis has been observed with chemotherapy treatment.

Cancer and its treatment can affect all three causes of thromboembolic disease, including the alteration of blood flow, damage to endothelial cells (the cells in blood vessels), and enhancing procoagulants (causing the blood to clot). Cancer can affect blood flow by mechanically affecting blood vessels close to a tumor. In addition, tumors cause angiogenesis, which may create complexes of blood vessels that have a disordered appearance and flow (varying in magnitude and direction). Chemotherapy or tumors may directly damage endothelial cells. Procoagulants may be secreted into the blood stream by cancer cells or can be increased on the surface of cancer cells.

Antithrombotic treatment, in the form of the low-molecular-weight heparin reviparin, has been shown for the first time to safely improve the outcomes of patients with an acute myocardial infarction. The new findings show that reviparin "clearly improves the outcomes of patients who undergo thrombolysis with streptokinase or urokinase, and it also appears to be a useful adjunct for patients treated with primary percutaneous coronary intervention [PCI]," said Dr. Anderson, associate chief of the division of cardiology at LDS Hospital in Salt Lake City. The study has some limitations.

Description

Heparin is the most common anticoagulant used and the generic name product may be available in the U.S. and Canada.

Mechanisms of action:

Heparin increases the release of specific proteins, like tissue plasminogen activator and tissue factor pathway inhibitor (TFPI), into the blood in order to inhibit blood coagulation. It can also increase the activity of these proteins. Heparin augments the activity of antithrombin III, a natural compound that inhibits activated clotting factors from contributing to more coagulation. Furthermore, heparin has been found to inhibit substances that may contribute to angiogenesis, including vascular endothelial growth factor, tissue factor, and platelet-activating factor.

Whether anticoagulants like heparin may also improve cancer survival rates independent of their effect on thromboembolism has been investigated. In fact, experimental and clinical data have demonstrated that heparin is an effective compound in preventing metastases. Many investigators have shown that heparin inhibits tumor **metastasis** in experimental animals; a few **clinical trials** also suggest a positive effect in humans with cancer.

Recommended dosage

Heparin is available only with a doctor's prescription, in parenteral and injection (United States and Canada) dosage forms. A doctor will need to prescribe a specific dose for an individual's based on the type of heparin, as well as the patient's medical condition and body weight.

Dosing schedule

Heparin should be taken under the doctor's direction and at the same time every day. If a dose is missed, take

it as soon as possible. However, if a dose is missed until the following day, patients should not double-dose, but just take the usual daily dose. Double-dosing may cause bleeding.

Precautions

Some medications should not be combined. Over-the-counter medicines, **vitamins**, and herbal products may cause interactions when combined with heparin, so the patient should check with the doctor monitoring the heparin medication before taking any new medication, even when prescribed by another doctor.

Patients who are pregnant, breastfeeding, have given birth recently, or using an IUD for birth control should consult their doctors. The doctor should also be notified if radiation treatments, surgery, or a fall or other injury has recently occurred.

The presence of other medical problems may affect the use of heparin. Patients should be sure to tell their doctors about any other medical problems, in particular:

- allergies or asthma (or history of)
- blood disease or bleeding problems
- colitis or stomach ulcer (or history of)
- diabetes mellitus
- high blood pressure (hypertension)
- kidney disease
- liver disease
- tuberculosis (active)

Side effects

The doctor should be contacted immediately if any of these side effects are present:

- wheezing or trouble breathing
- skin rash, **itching**, or hives
- red or "coffee ground" vomit
- unexplained nosebleeds
- swelling in the face, lips, or tongue
- blood in urine or stools
- black tarry stools

Interactions

Using any of the following medicines together with heparin may increase the risk of bleeding. Again, candidates for heparin should alert their physicians if they are taking any of these medications:

- aspirin
- persantine
- carbenicillin by injection (Geopen)
- cefamandole (Mandol)
- cefoperazone (Cefobid)
- cefotetan (Cefotan)
- dipyridamole (Persantine)
- divalproex (Depakote)
- medicine for inflammation or pain (Motrin, Aleve), except narcotics
- medicine for overactive thyroid
- pentoxifylline (Trental)

KEY TERMS

Angiogenesis—The formation of new blood vessels that occurs naturally under certain circumstances, for example, in the healing of a cut.

Anticoagulant—Anticoagulants are nonhabit-forming medications that prevent the formation of new blood clots and keep existing blood clots from growing larger.

Blood clot—A clump of blood that forms in or around a vessel as a result of coagulation. The formation of blood clots when the body has been cut is essential because without blood clots to cease the bleeding, a person would bleed to death from a relatively small wound.

Coagulation—The blood's natural tendency to clump and stick.

Embolism—An embolism occurs when a clump of material such as a broken-off piece of plaque, a blood clot, or air travels through the bloodstream and becomes lodged in a blood vessel.

Endothelial cells—The cells lining the inside of blood vessels.

Parenteral—Medications administered through intravenous, subcutaneous, or intramuscular injection.

Procoagulants —Inducing the blood to clot.

Thromboembolism—Another word for embolism (see embolism).

Thrombosis—The formation of a blood clot in an artery or vein that may be accompanied by inflammation. If untreated in arteries, thrombosis can lead to death of the nearby tissue.

- plicamycin (Mithracin)
- probenecid (Benemid)
- sulfinpyrazone (Anturane)
- ticarcillin (Ticar)
- valproic acid (Depakene)
- medicines via intramuscular injection

See also Low molecular weight heparin; Warfarin.

Crystal Heather Kaczkowski, MSc.

Hepatic arterial infusion

Definition

Hepatic arterial infusion (HAI) therapy, delivers chemotherapeutic agents directly to the liver through a catheter placed in the hepatic artery. The hepatic artery is the main route of blood supply to liver tumors. HAI is also known as regional **chemotherapy**.

Purpose

Approximately 160,000 patients are diagnosed with **colon cancer** in the U.S. each year. The cancer spreads to the liver in about 70 percent of those patients. For patients with colorectal liver metastases, tumor progression within the liver is typically the primary cause of death.

Systemic chemotherapy using various agents has some efficacy, but the side effects can have a profound negative impact on the patient's quality of life during treatment. HAI therapy may be an effective option because it delivers chemotherapy medication directly to the site of the tumor, making it appropriate as an alternative or adjuvant treatment to systemic chemotherapy. When metastases is limited to the liver, HAI with **floxuridine** (FUDR) or radioactive microspheres through an implantable pump under the skin or an external pump worn on the belt may be a better option than systemic chemotherapy.

HAI may extend life expectancy and reduce the chance that more liver tumors will develop.

Precautions

- Strict aseptic techniques should be used to prevent infection during all procedures.
- Pump flow rate will vary depending on factors such as body temperature, altitude, arterial pressure at the catheter tip, and solution viscosity.
- Patients should not attempt to resterilize the pump.
- The manufacturer's instructions should be followed regarding drug preparation, dosage, and administration.
- FUDR should be used with added caution in patients with impaired liver or kidney function.

Systemic therapy should be considered for patients with disease known to extend beyond the area capable of being infused.

Description

HAI enhances cancer therapy by increasing drug delivery directly to the site of the tumor (the liver) while minimizing systemic drug exposure and side effects. Development of fully implanted infusion systems have allowed for long-term delivery of hepatic regional chemotherapy.

Benefits of HAI therapy:

- yields higher tumor response rates and delays cancer progression
- trend toward increased survival rates
- enhances quality of life
- reduced systemic side effects

Preparation

Patient selection criteria

Successful results depend on careful patient selection. Candidates for HAI therapy should:

- have primary liver cancer or liver metastases from primary colorectal cancer
- show an absence of tumors outside the liver
- have demonstrated portal vein patency
- be a suitable surgical candidate
- show no evidence of infection
- be willing to participate in frequent pump refill appointments

Studies have demonstrated that patients with metastatic colorectal cancer who had liver disease only, had less than 70% of their liver involved with metastases, and had a good performance status responded best to HAI. When metastases are also located outside of the liver, HAI does not offer an advantage over systemic chemotherapy.

KEY TERMS

Adjuvant treatment—A treatment that is added to increase effectiveness of the first treatment.

Cancer—A term for diseases in which abnormal cells divide without control. Cancer cells can invade nearby tissues and can spread through the bloodstream and lymphatic system to other parts of the body.

Catheter—A flexible tube used to administer or withdraw fluids. During a course of chemotherapy, an indwelling catheter can be placed in a vein to administer intravenous fluids and chemotherapy. Catheters can stay in place for several weeks or months with proper care.

Chemotherapy—A cancer treatment using medicines.

Hepatic—Refers to the liver.

Implant—A device inserted into the body to either treat cancer or to replace or substitute for a lost part or ability.

Metastases—The spread of cancer to other body parts.

Tumor—An abnormal mass of tissue that serves no purpose. Tumors may be either benign (non-cancerous) or malignant (cancerous).

Aftercare

During the course of treatment, pump pocket infections occur rarely. At the first sign of infection at the pump pocket, systemic **antibiotics** need to be started. The pump needs to be moved to a new location in a newly created pocket if the infection does not resolve itself. The old pocket should be opened and drained.

Risks

The major problems with HAI are not surgical. They include gastritis, duodenitis, and biliary sclerosis.

Drug toxicity and medication side effects may occur. The most commonly reported side effects for FUDR are nausea and vomiting, **diarrhea**, and intestinal inflammation.

Other possible complications include:

- Arterial thromboses.
- Catheter dislodgement.
- The catheter may erode through the wall of the duodenum when the pump has been in place for more than a year.
- Overdose or underdose of medication if certain conditions affect the rate at which the pump delivers medication, i.e. pump damage due to strenuous activity, high heat, or a change in air pressure.
- Disruption in therapy if the pump is damaged by improper handling or filling.

Normal results

Morbidity or mortality occurring as a result of this procedure should be close to zero. Appropriate selection of patients and new combinations of chemotherapy should provide at least a 70% response rate from HAI for the treatment of hepatic metastases from colorectal primary tumors. This response rate is at least twice that of current systemic chemotherapies.

When used in conjunction with traditional chemotherapy, HAI therapy has been shown to extend life expectancy and reduce recurrence of liver tumors after two years for certain patients.

Abnormal results

Complications that can occur with surgery:

- infection
- fluid build up around the implant site
- skin erosion over the site of the implant
- incision breakdown
- drugs may be delivered to organs other than the liver

Resources

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Hepatocellular carcinoma *see* **Liver cancer, primary**

Herceptin

Definition

Herceptin is a medicine that is used to slow or stop the growth of a cancerous tumor.

Purpose

Herceptin is used to treat **breast cancer** that has spread to other parts of the body in women whose tumor cells produce an overabundance of a protein known as the human epidermal growth factor receptor 2 (HER2).

Description

Also known by its generic name, **trastuzumab**, Herceptin is an antineoplastic drug manufactured by Genentech, Inc. A monoclonal antibody, Herceptin works differently than **chemotherapy** or hormonal anticancer drugs. It targets cancer cells that make too much of the HER2 protein, which is found on the surface of the cancer cells and thought to fuel cancer growth. Used only to treat cancers that make an overabundance of HER2 protein, Heceptin works by binding to the protein's particles and blocking its effect, thereby slowing down or stopping the cancer cell growth. The HER2 proteins with Herception are removed from the surface the cell. When this happens, they cannot tell the cell to grow and divide.

In addition, Genentech, Inc. explains that there may be two other factors that account for Herceptin's effectiveness; Herceptin signals the immune system and works with chemotherapy. After Herceptin binds to the HER2 protein, the natural killer cells of the immune system are attracted to Herceptin. Herceptin, in turn, binds to the natural killer cells and determines which cells are abnormal and helps to kill them. When this occurs, chemotherapy may be ehanced. Although Herceptin and chemotherapy work differently, Genentech points out that when used together, "the two drugs can be synergistic. Treatment with Herceptin prevents DNA repair following the impact of DNA-damaging chemotherapy that stops the tumor cells from growing."

According to the National Cancer Institute, approximately 25–30% of breast cancers make too much HER2 protein. These kinds of tumors tend to grow faster and are more likely to recur. The amount of HER2 that is present in a tumor is determined by a lab test and a score from 0, which is a negative score, to 3+, which is a highly positive score, is assigned. Only patients with high scores are expected to benefit from Herceptin treatment.

Clinical Trial Results and FDA Approval

Two groundbreaking **clinical trials** were conducted to test the safety and efficacy of Herceptin. One of them, conducted by Slamon and colleagues, produced data that led to Herceptin's approval by the U.S. Food and Drug Administration (FDA) in 1998. In 2001, The *New England Journal of Medicine* published the study results by Slamon and colleagues, which involved 234 randomly assigned patients who received chemotherapy alone and 235 patients who received chemotherapy plus Herceptin. All the patients in the study were diagnosed with metastasic breast cancer that overproduced HER2. Ultimately, Slamon and colleagues concluded that the addition of Herceptin to chemotherapy was associated with "a longer time to disease progression, a higher rate of response [to the treatment], longer survival, and a 20% reduction in the risk of death," as compared to treatment with chemotherapy alone. Specifically, for example, Herceptin combined with **paclitaxel** proved to be especially valuable; the overall response rate rose from 15% in women treated with paclitaxel to 38% in women treated with Herceptin and paclitaxel. All factors considered Herceptin seems to increase the clinical benefits of first-line chemotherapy.

In another clinical trial, as explained by the National Cancer Institute, "Women were given only Herception. In 14% of these women, the tumor got smaller or disappeared." Therefore, in September 1998, the FDA announced its approval of Herceptin for the treatment of metastatic breast cancer. Herceptin was specifically approved in combination with paclitaxel as therapy for HER2 breast cancer. It is also used alone as a therapy after other therapies have failed." Used by itself or with chemotherapy, Herceptin is the first FDA-approved therapy that targets a particular genetic defect known to play a role in cancer development.

Other Possible Uses for Herceptin

Herceptin is also being studied as an adjuvant therapy for the treatment of nonmetastatic breast cancer that has spread to the lymph nodes, but not anywhere else.

Herceptin may also be useful in fighting cancers of the lung, colon, prostate, and bladder in patients whose tumors have an overabundance of HER2. Several studies are underway to test the effectiveness of Herceptin with and without other anticancer drugs.

Recommended dosage

Herceptin is administered intravenously on a weekly basis in a hospital or clinic setting. Based on the patient's

body weight, the typical dosage is 0.9 to 3.6 mg per pound.

Precautions

It is important to have periodic blood tests while taking Heceptin, because it can cause **anemia** and a low white blood cell count in many patients. Guarding the cardiac health of patients taking Herceptin is imperative, because using it can lead to congestive heart failure. Therefore, some patients may not be able to take Herceptin.

It isn't known whether Herceptin is safe to take while a patient is pregnant. Nonetheless, patients should avoid becoming pregnant while they are taking Herceptin. Pregnant patients should talk with their physicians regarding any possible risks to the fetus. Mothers should not breastfeed their babies while they are being treated with Herceptin, because it does pass to the breast milk. In fact, mothers should not breastfeed for at least 6 months after being treated with Herceptin.

Side effects

The two most serious side effects associated with the use of Herceptin are cardiac amd lung related. Damage to the heart muscle, which can cause heart failure, and lung complications, which can cause serious breathing problems can occur. In both cases, immediate medical attention is required. Whether during or after treatment, patients experiencing difficulty breathing or any of the signs associated with heart failure, such as shortness of breath, a fast heartbeat, or swelling in the feet or legs, should contact their physicians without delay. Cardiac side effects are more frequently experienced by elderly patients. Also, in clinical trials, it was found that patients receiving Herceptin with anthracycline chemotherapy were more likely to experience cardiac dysfunction than those who did not receive anthracyclines. Patients treated with Herceptin must be monitored carefully and screened prior to their treatment for any lung or heart problems. It is sometimes necessary to discontinue treatment with Herceptin.

The National Cancer Institute cautions patients that Herceptin can cause severe allergic reactions, such as low blood pressure, shortness of breath, rashes, and wheezing. These reactions are usually more common in patients who already suffer from lung disease.

Fever and chills are common during the first infusion and occur less frequently thereafter. Throughout Herceptin treatment it is not uncommon for patients to experience nausea, vomiting, **diarrhea**, dizziness, sleeplessness, appetite loss, cough, abdominal and back pain, headache, and sore throat. **Depression**, tingling in the hands or feet, fluid retention, sinus irritation, and flu-like symptoms are less commonly reported. Uncommon side effects are acne, cold sores, and urinary infection, as well as pain in the joints, bones, or nerves. As reminded by the National Cancer Institute, it is important to note that patients being treated with Herceptin alone in comparison to patients being treated with Herceptin and chemotherapy may have different side effects. For example, when Herceptin is used in combination with chemotherapy, patients are more likely to experience anemia leukopenia, diarrhea, and infection. Therefore, blood tests may be required more frequently for patients being treated with both Herceptin and chemotherapy. Rare side effects can develop in any part of the body, however, regardless of whether a patient is being treated with Herceptin only or in combination with chemotherapy. Patients should inform their physicians when they experience any side effects, regardless of whether the side effects are mild or severe. Some side effects, such as pain, can be managed medically.

Whether in the early or advanced stages, cancer itself can cause pain. In fact, numerous studies, such as the one by Reuben and colleagues published in 1998 in the Archives of Internal Medicine, have validated that patients with advanced cancer are likely to have a number of symptoms in addition to pain, such as insomnia, depression, and **fatigue**. Therefore, it is valuable, if possible, to determine the source of the pain whether it is the drug therapy or the cancer itself causing the pain. Once the source of the pain is determined, it is easier to decide what the next course of action should be. Patients should be their own health care advocates and work as closely as possible with their physicians regarding treatment strategies for adverse side effects and cancer-related pain. Patients should talk with their physicians about a variety of treatment modalities that range from conventional options to alternative therapies, such as acupuncture, for example.

Pain intensity should also be considered when developing a treatment plan to cope with unpleasant side effects. Certain pain measurement tools, such as the Visual Analogue Pain Scale (VAPS) and the McGill Pain Questionnaire, are commonly used by physicians to assess pain intensity. Patients having difficulty coping with the pain associated with cancer and cancer drugs might find it helpful to be referred to a physician who specializes in **pain management** or a painclinic. Physicians specializing in the treatment of pain come from a variety of medical backgrounds, such as anesthesiology, obstetrics and gynecology, neurology, and surgery.

KEY TERMS

Adjuvant therapy—Adjuvant therapy is treatment given in addition to the primary therapy.

Metastatic cancer—Cancer that has spread from the place in which it started to other parts of the body.

Because of the complicated nature of cancer and cancer-related pain, ideally a pain management team should be formed that works with the patient's primary care physician, oncologist, and radiologist to provide comprehensive care to the patient.

Advances in cancer treatment lengthen survival among cancer patients. It is important for cancer patients to understand that they are not alone. Support groups exist to help patients cope not only with the physical aspects of having cancer, but with the psychological ones as well. In addition, the positive support (both emotional and otherwise) provided by caregivers can help to improve a patient's quality of life.

Interactions

There are no known food interactions. However, as mentioned earlier, cardiac dysfunction was especially high in patients who received Herceptin in combination with anthracycline chemotherapy. Patients should discuss any medications (over-the counter, herbal, and prescription) that they are taking with their physician so that an assessment can be made regarding the risk of interactions.

There are, in fact, a multitude of precautions and interactions related to chemotherapy treatment. The best thing for patients to do that are undergoing chemotherapy is to discuss all the precautions and interactions with their physicians. Usually a patient's doctor will provide patient education pamphlets regarding chemotherapy treatment. Pamphlets are also available from local cancer centers and the American Cancer Society.

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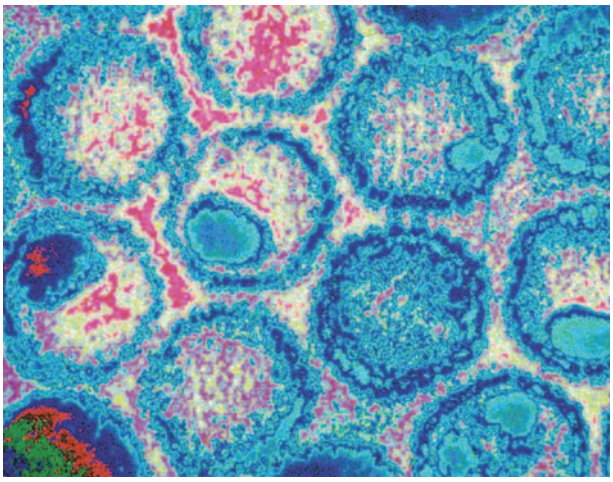
Lee Ann Paradise

Herpes simplex

Description

Herpes simples virus (HSV, or herpesvirus) is a virus that causes infection of skin and mucous membrane and rarely infects other parts of the body. However, in the immunosuppressed patient, HSV may cause **pneumonia** and other more severe infections. When the infection occurs in the mouth it is commonly referred to as cold sores. An outbreak of HSV infection can be very painful. There are two distinct types of HSV: type 1 and type 2. It was believed that HSV-1 mostly caused oral herpes (herpes labialis), while HSV-2 generally caused genital herpes that typically affects the penis, vulva, and rectum. This is not completely true. Both type 1 and type 2 can cause herpes lesions on the lips or genitals. The first symptoms occur within 2-20 days after contact with an infected person.

Symptoms of the primary infection are usually more severe than those of recurrent infections. The primary infection can cause symptoms like those experienced in other viral infections, including lack of energy, headache, **fever**, and swollen lymph nodes in the neck. The first sign of infection is formation of fluid-filled blisters that may last up to two weeks. However, the pain in the area may last much longer. Once HSV enters the body it spreads to nearby mucosal areas through nerve cells. Once it infects the body the virus remains latent for the life of that individual. During the period of latency there are no symptoms. At times the infected person may shed



Color digitized electron micrograph image of herpes simplex virus. Cancer patients, especially those who are undergoing chemotherapy or radiation treatments, are at greater risk of herpes infections. *(Custom Medical Stock Photo. Reproduced by permission.)*

the virus, even in the absence of visible symptoms, and infect others. Individuals infected with the virus can have recurrent infections; however, normally, recurrent infections are milder and shorter. However, cancer patients can have severe recurrences.

Typically, 50–80% of persons with oral herpes experience a prodrome (symptoms of oncoming disease) of pain, burning, **itching**, or tingling at the site where blisters will form. This prodrome stage may last anywhere from a few hours to one to two days. The herpes infection prodrome occurs in both the primary infection and recurrent infections.

Causes

Everyone with cancer has a higher risk of catching viral infections of any type. This is because the cancer itself, and the methods used to treat it, affect the immune defense mechanisms that fight infection. Normally the mucous membrane is one of the first lines of defense against infectious organisms. However, **chemotherapy** and radiation can damage this very important barrier. The barrier that skin provides is also compromised because of needles used for drawing blood or injecting drugs. Radiation and chemotherapy also suppress the immune system. Certain cancers like Hodgkin's disease, lymphoma, and T-cell leukemia cause defects in cellular immunity, which is a primary defense mechanism against viral infections. Thus cancer patients, especially those who are undergoing chemotherapy or radiation treatments, are at greater risk of primary and secondary herpes infections.

Oral herpes simplex infections are more common in children than adults following chemotherapy. Patients who have the virus latent in the system have a higher chance of recurrent infection. Primary infection generally causes gingivitis (inflammation of the gums, vesicles on the mucosa (blisters on the lining of the mouth), and a coated tongue (white covering on tongue). Women with genital herpes can have severe recurrence following chemotherapy because of immunosuppression.

Treatment

There is no cure for HSV infection although there are antiviral drugs available that have some effect in lessening the symptoms and decreasing the length of herpes outbreaks. There is evidence that some of these drugs may also prevent future outbreaks. For the best results drug treatment should begin during the prodrome stage before blisters are visible. Depending upon the length of the outbreak, drug treatment could continue up to 10 days.

Acyclovir (Zovirax) is the drug of choice for herpes infection and can be given intravenously or taken by mouth. It can be applied directly to sores as an ointment but is not very useful in this form. A liquid form for children is also available. Acyclovir is effective in treating both the primary infection and recurrent outbreaks. When taken by mouth to prevent an outbreak, acyclovir reduces the frequency of herpes outbreaks.

Alternative and complementary therapies

A number of steps can relieve the symptoms of herpes infections. It is important to keep the blisters or sores clean and dry with an agent like cornstarch. One should avoid touching the sores, and wash hands frequently. Local application of ice may relieve the pain. Over-the-counter medication for fever, pain, and inflammation—such as aspirin, acetaminophen, or ibuprofen—may help. Children should never be given aspirin. Sexual intercourse should be avoided during both the active stage and the prodrome stages. During an outbreak of cold sores salty foods, citrus foods (oranges etc.), and other foods that irritate the sores should be avoided. Over-the-counter lip products that contain the chemical "phenol" (such as Blistex Medicated Lip Ointment) and numbing ointments (such as Anbesol) help to relieve the pain of cold sores. A bandage may be placed over the sores to protect them and prevent spreading the virus to other sites on the lips or face.

A diet rich in the amino acid lysine may help prevent recurrences of cold sores. Foods that contain high levels of lysine include most vegetables, legumes, fish, turkey,

and chicken. Oral lysine supplements in the amount of 1000 mg per day may help sores heal faster. There is a belief that foods with high lysine-to-arginine ratio will help prevent outbreaks of herpes simplex. That has not been proven, and it is important to include foods that have a low lysine-to-arginine ratio also, such as nuts, onion, garlic, and green vegetables. It is also suggested that the amount of arginine in the diet be limited as there is a belief that arginine is needed for herpesvirus growth. This amino acid is found in peanuts, beer, chocolate, gelatin, and raisins.

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Herpes zoster

Description

Herpes zoster, also called shingles, and referred to as "zosteer", gets its name from both the Latin and French words for belt or girdle and refers to belt-like skin eruptions that may occur on the trunk of the body. The virus that causes chickenpox, the varicella zoster virus (VSV), can become dormant in nerve cells after an episode of chickenpox and later re-emerge as shingles. Any individual who has had chickenpox can develop shingles. People of all ages, even children, can be affected, but the incidence increases with age. There are many other conditions which can predispose people to developing shingles, including newborn infants, bone marrow and other transplant recipients, and individuals with immune systems weakened by diseases like HIV or cancer, or drugs, such as those used in **chemotherapy**.

Shingles erupts along the course of the affected nerve, producing lesions anywhere on the body and may cause severe nerve pain. The most common areas to be affected are the face and trunk, which correspond to the areas where the chickenpox rash is most concentrated. The disease is caused by a reactivation of the chickenpox virus that has been dormant in certain nerves following an episode of chickenpox. Exactly how or why this reactivation occurs is not clear; however, it is believed that the reactivation is triggered when the immune system becomes weakened as in the examples described above. Early signs of shingles are often vague and can easily be mistaken for other illnesses. The condition may begin with **fever** and malaise (a vague feeling of weakness or discomfort). Within two to four days, severe pain, **itching**, and numbness/tingling (paresthesia) or extreme sensitivity to touch (hyperesthesia) can develop, usually on the trunk and occasionally on the arms and legs. Pain may be continuous or intermittent, usually lasting from one to four weeks. It may occur at the time of the eruption, but can precede the eruption by days, occasionally making the diagnosis difficult. Signs and symptoms may include the following:

- itching, tingling, or severe burning pain
- red patches that develop into blisters
- grouped, dense, deep, small blisters that ooze and crust
- swollen lymph nodes

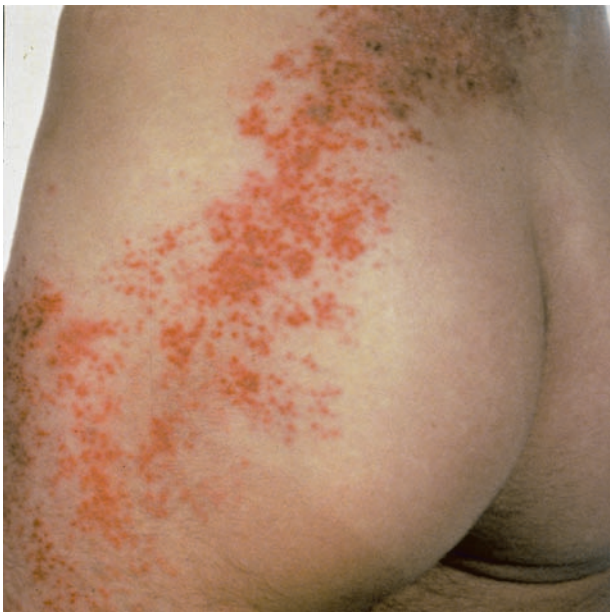
Immunocompromised patients usually have a more severe course that is frequently prolonged for weeks to months. They develop shingles frequently and the infection can spread to the skin, lungs, liver, gastrointestinal tract, brain, or other vital organs.

Potentially serious complications can result from herpes zoster. Many individuals continue to experience persistent pain long after the blisters heal. This pain, called post-herpatic neuralgia, can be severe and debilitating. Post-herpetic neuralgia can persist for months or years after the lesions have disappeared.

Other complications include a secondary bacterial infection, and rarely, potentially fatal inflammation of the brain (encephalitis) and the spread of an infection throughout the body. These rare, but extremely serious, complications are more likely to occur in those individuals who have weakened immune systems (immunocompromised).

Causes

Herpes zoster has been reported in patients with many different types of cancer. However, the cancers that affect an individual's immune system, such as leukemia or **lymphoma**, are the types that place people at particular risk. Herpes zoster is also a particular problem after the various forms of cancer therapy. A study performed in 1998 looked at 766 episodes of herpes zoster infection at a large cancer center from 1972 to 1980. The highest risk of infection was present among patients with lymphoma and leukemia. In those who received radiation treatment and then developed herpes zoster, half of them developed this within seven months. They



Shingles, or herpes zoster, on patient's buttocks and thigh. *(Custom Medical Stock Photo. Reproduced by permission.)*

developed zoster on the area of their body where the radiation was given. This study showed that a period of months can pass before developing zoster as a consequence of radiation. In those who developed zoster after being treated with chemotherapy, half of them developed zoster within a month.

A study in 1999 looked at 215 consecutive patients who had received high-dose chemotherapy and autologous stem cell rescue to help determine what the incidence and severity of herpes zoster infection was. Herpes zoster was developed in 40 people. Over 80% of these infections occurred within six months of receiving the autologous stem cell rescue. Similar rates of herpes zoster have been seen in patients who received bone marrow transplants. A 1996 study looked at 107 children who had received bone marrow transplants for various malignancies. Thirty-three percent of these children developed herpes zoster. Approximately 90% of the cases developed within one year from the time of bone marrow transplant.

Treatments

Shingles almost always resolves spontaneously and may not require any treatment except for the relief of symptoms. In most people, the condition clears on its own in one or two weeks and seldom recurs. The antiviral drugs acyclovir, valacyclovir, and famciclovir can be used to treat shingles. These drugs may shorten the course of the illness. Their use results in more rapid healing of the blisters when drug therapy is started within 72 hours of the onset of the rash. In fact, the earlier the drugs are administered, the better, because early cases can sometimes be stopped. If taken later, these drugs are less effective but may still lessen the pain. Antiviral drug treatment does not seem to reduce the incidence of post-herpetic neuralgia, but recent studies suggest famciclovir may cut the duration of post-herpetic neuralgia in half. Side effects of typical oral doses of these antiviral drugs are minor with headache and nausea reported by 8-20% of patients. Severely immunocompromised individuals, such as those with cancer, may require intravenous administration of antiviral drugs. Preventive administration of acyclovir to seropositive patients (people who have evidence in their blood of past infection with varicella) who undergo leukemia induction or bone marrow transplant not only effectively prevents herpes zoster recurrence but also reduces the severity of chemotherapy-induced **mucositis**. Therefore, acyclovir prophylaxis should be considered in seropositive patients, especially if they have had a recurrence during previous chemotherapy cycles.

Alternative and complementary therapies

Cool, wet compresses may help reduce pain. If there are blisters or crusting, applying compresses made with diluted vinegar will make the patient more comfortable. The patient can mix one-quarter cup of white vinegar in two quarts of lukewarm water, and use the compress twice each day for 10 minutes. The patient should stop using the compresses when the blisters have dried up.

Soothing baths and lotions such as colloidal oatmeal baths, starch baths or lotions, and calamine lotion may help to relieve itching and discomfort. The skin should be kept clean, contaminated items should not be re-used. While the lesions continue to ooze, the person should be isolated to prevent infecting other susceptible individuals.

Later, when the crusts and scabs are separating, the skin may become dry, tight, and cracked. If that happens, the patient can rub on a small amount of plain petroleum jelly three or four times a day.

There are non-medical methods of prevention and treatment that may speed recovery. For example, getting lots of rest, eating a healthy diet, exercising regularly, and minimizing stress are always helpful in preventing disease. Supplementation with vitamin B_{12} during the first one to two days and continued supplementation with vitamin B complex, high levels of vitamin C with bioflavonoids, and calcium, are recommended to boost the immune system. Herbal antivirals such as echinacea can be effective in fighting infection and boosting the immune system. Patients should consult physician before taking supplements.

KEY TERMS

Acyclovir—An antiviral drug that is available under the trade name Zovirax, in oral, intravenous, and topical forms. The drug blocks the replication of the varicella zoster virus.

Antibody—A specific protein produced by the immune system in response to a specific foreign protein or particle called an antigen.

Famciclovir—An oral antiviral drug that is available under the trade name Famvir. The drug blocks the replication of the varicella zoster virus.

Immunocompromised—A state in which the immune system is suppressed or not functioning properly.

Post-herpetic neuralgia—The term used to describe the pain after the rash associated with herpes zoster is gone.

Valacyclovir—An oral antiviral drug that is available under the trade name Valtrex. The drug blocks the replication of the varicella zoster virus.

Although no single alternative approach, technique, or remedy has yet been proven to reduce the pain, there are a few options which may be helpful. For example, topical applications of lemon balm (*Melissa officinalis*) or licorice (*Glycyrrhiza glabra*) and peppermint (*Mentha piperita*) may reduce pain and blistering. Homeopathic remedies include *Rhus toxicodendron* for blisters, *Mezereum* and *Arsenicum album* for pain, and *Ranunculus* for itching. Practitioners of Eastern medicine recommend self-hypnosis, acupressure, and acupuncture to alleviate pain. All of these or similar alternative therapies should be discussed with the treating physician before using.

See also Antiviral therapy.

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David Greenberg, M.D.

Hickmann lines *see* **Vascular access**

Histamine 2 antagonists

Definition

Histamine 2 antagonists are drugs that block the production of acid in the stomach.

Purpose

Histamine 2 antagonists are used to treat the precancerous condition of **Barrett's esophagus**. They are also used to treat **Zollinger-Ellison syndrome** and multiple endocrine neoplasia, rare cancerous conditions in which the stomach makes too much acid and to prevent the development of gastric (stomach) and duodenal (upper part of the small intestine) ulcers.

Description

Histamine 2 blockers are familiar to most people as the over-the counter heartburn medications Tagamet (cimetidine), Pepcid, (famotidine), and Zantac (ranitidine). Axid (nizatidine) is less well known. These drugs also come in prescription strengths. Histamine 2 blockers work by reducing the amount of acid the stomach produces.

The esophagus is a tube 10–13 inches long and about 1 inch wide that carries food from the mouth to the stomach. Normally, the esophagus is lined with cells that are similar to skin cells and look smooth and pinkish-white.

The stomach makes acid to help digest food. A different type of cell that is resistant to acid lines the stomach. These cells look red and velvety. At the place where the esophagus meets the stomach, there is a ring of muscle called a sphincter that normally keeps acid stomach juices from backflowing into the esophagus. When this sphincter is not working correctly, stomach acid enters the bottom portion of the esophagus. This backflow is called reflux or heartburn. When reflux occurs frequently over an extended period of time, it is called gastroesophageal reflux disease (GERD).

Barrett's esophagus is a pre-cancerous condition in which normal cells lining the esophagus are repeatedly exposed to stomach acid and are replaced with abnormal cells that, in some people, develop into a type of cancer of the esophagus called adenocarcinoma. Histamine 2 blockers are given to reduce acid in the stomach and eliminate exposure of the esophageal cells to acid.

Histamine 2 blockers are also used to treat two rare cancerous conditions: multiple endocrine neoplasia (MEN) and Zollinger-Ellison syndrome, both of which

can cause the stomach to produce too much acid. In MEN, an inherited form of cancer, tumors form in more than one gland. Depending on which glands are affected, the stomach may be stimulated to produce excess acid. In Zollinger-Ellison syndrome, a tumor in the digestive tract secretes a hormone called gastrin that stimulates the production of stomach acid. These tumors are malignant (cancerous) in 50% to 65% of people with Zollinger-Ellison syndrome.

Histamine 2 blockers are sometimes given in advance of **chemotherapy** to help reduce the gastrointestinal side effects of chemotherapy drugs. Cimetidine was the first histamine 2 blocker approved by the United States Food and Drug Administration (FDA) in 1976.

Recommended dosage

Recommended dose varies depending on how much stomach acid is produced. Histamine 2 blockers are available in low doses without a prescription and in higher doses with a prescription. They are available in tablet, chewable tablet, liquid, and injectable liquid form. In 2004, the FDA also approved a 25 mg effervescent tablet form of ranitidine (Zantac 25 Efferdose). If histamine 2 inhibitors are unsuccessful in controlling acid reflux, proton pump inhibitors (Prevacid, Prilosec) are usually given as an alternative.

Precautions

People who have trouble with heartburn should stay away from acidic foods such as orange, grapefruit, and tomato juice, coffee, and carbonated drinks (sodas) because these all increase stomach acid. Waiting at least two hours after eating before lying down, avoiding smoking, limiting drinking of alcohol, losing excess weight, and avoiding wearing tight-fitting clothes are other ways to prevent heartburn. Although animal studies show that histamine 2 blockers appear to be safe during pregnancy, these drugs pass into breast milk and should not be taken by nursing mothers.

Side effects

Histamine 2 blockers have few side effects. These drugs are excreted by the kidney, and may slow the excretion of other drugs excreted by the kidney. People with reduced kidney function may need a reduced dose of histamine 2 blockers.

Rare cases of irregular heart rhythms and high blood pressure have been reported when histamine 2 blockers are given intravenously (IV, injected directly into a vein). Mild **diarrhea** has been reported by some people taking these drugs.

KEY TERMS

Esophagus—The canal between the pharynx and stomach that allows passage of food and liquids.

Gastrointestinal—Pertaining to the stomach and intestine.

Interactions

Histamine 2 blockers are reported to have few interactions with other drugs. However, because they reduce the level of acid in the stomach, they may inhibit the uptake of drugs such as ketoconazole that depend on an acid environment in the stomach to work. These drugs should be administered at least two hours before histamine 2 blockers are taken. Prior to starting any over-the-counter medications, herbal medications, or new medications, patients should notify their physician and check with their pharmacists for any potential drug interactions.

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Teresa G. Odle

Histiocytosis X

Definition

Histiocytosis X is a generic term that refers to an increase in the number of histiocytes, a type of white blood cell, that act as scavengers to remove foreign material from the blood and tissues. Since recent research demonstrated Langerhans cell involvement as well as histiocytes, this led to a proposal that the term Langerhans Cell Histiocytosis (LCH) be used in place of histiocytosis X. Either term refers to three separate illnesses (listed in order of increasing severity): eosinophilic granuloma; Hand-Schuller-Christian disease; and Letterer-Siwe disease.

Description

Epidermal (skin) Langerhans cells (a form of dendritic cell) accumulate with other immune cells in various parts of the body and cause damage by the release of chemicals. Normally, Langerhans cells recognize foreign material, including bacteria, and stimulate the immune system to react to them. Langerhans cells are usually found in skin, lymph nodes, lungs, and the gastrointestinal tract. Under abnormal conditions these cells affect skin, bone, and the pituitary gland as well as the lungs, intestines, liver, spleen, bone marrow, and brain. Therefore, the disease is not confined to areas where Langerhans cells are normally found. The disease is more common in children than adults and tends to be most severe in very young children.

Histiocytosis X or LCH is a family of related conditions characterized by a distinct inflammatory and proliferative process but differs from each other in which parts of the body are involved. The least severe of the histiocytosis X/LCH family is eosinophilic granuloma. Approximately 60–80% of all diagnosed cases are in this classification, which usually occurs in children aged 5–10 years. The bones are involved 50–75% of the time, which includes the skull or mandible, and the long bones. If the bone marrow is involved, **anemia** can result. With skull involvement, growths can occur behind the eyes, bulging them forward. One recent case study involved swelling of the eyes caused by histiocytosis in a three-year-old girl. The lungs are involved less than 10% of the time, and this involvement signals the worst prognosis.

Next in severity is Hand-Schuller-Christian disease, a chronic, scattered form of histiocytosis. It occurs most commonly from the age of one to three years and is a slowly progressive disease that affects the softened areas of the skull, other flat bones, the eyes, and skin. Letterer-Siwe disease is the acute form of this series of diseases. It is generally found from the time of birth to one year of age. It causes an enlarged liver, bruising and skin lesions, anemia, enlarged lymph glands, other organ involvement, and extensive skull lesions.

Causes and symptoms

This is a rare disorder affecting approximately 1 in 200,000 children or adults each year. The International Histiocyte Society formed a registry in 2000 that has registered a total of 274 adults from 13 countries as of 2003. Because histiocytic disorders are so rare, little research has been done to determine their cause. Over time, histiocytosis may lessen in its assault on the body but there are still problems from damage to the tissues. There are no apparent inheritance patterns in these diseases with the exception of a form involving the lymphatic system; of the 274 adults in the international registry, only one came from a family with a history of the disease.

The symptoms of histiocytosis are caused by substances called cytokines and prostaglandins, which are normally produced by histiocytes and act as messengers between cells. When these chemicals are produced in excess amounts and in the wrong places, they cause tissue swelling and abnormal growth. Thus, symptoms may include painful lumps in the skull and limbs as well as rashes on the skin. General symptoms may include: poor appetite, failure to gain weight, recurrent **fever**, and irritability. Symptoms from other possible sites of involvement include:

- Gums: swelling, usually without significant discomfort.
- Ear: chronic discharge.
- Liver or spleen: abdominal discomfort or swelling.
- Pituitary: This gland at the base of the brain is affected at some stage in approximately 20%–30% of children causing a disturbance in water balance to produce thirst and frequent urination.
- Eyes: Due to the bony disease, behind-the-eye bulging may occur (exophthalmos).
- Lungs: Breathing problems.

Diagnosis

The diagnosis can be made only by performing a **biopsy**, that is, taking a tissue sample under anesthesia from a site in the patient thought to be involved. Blood and urine tests, chest and other x rays, **magnetic resonance imaging** (MRI) and **computed tomography** scans (CAT scans) (to check the extent of involvement), and possibly bone marrow or breathing tests may be required to confirm the diagnosis.

Treatments and prognosis

Although this disease is not cancer, most patients diagnosed with it are treated in cancer clinics. There are two reasons for this:

- Historically, cancer specialists treated it before the cause was known.
- The treatment requires the use of drugs typically required to treat cancer.

Any cancer drugs utilized are usually given in smaller doses, which diminishes the severity of their side effects. **Radiation therapy** is rarely used, and special drugs may be prescribed for skin symptoms. If there is

KEY TERMS

Anemia—Abnormally low level of red blood cells in the blood.

Biopsy—Surgical removal of tissue for examination.

CT or CAT—Computed tomography, a radiologic imaging that uses computer processing to generate an image of tissue density in slices through the patient's body.

Cytokines—The term used to include all protein messengers that regulate immune responses.

Dendritic—Branched like a tree.

Eosinophils—A leukocyte with coarse, round granules present.

Epidermal—The outermost layer of the skin.

Inflammatory—A localized protective response of the body caused by injury or destruction of tissues.

MRI—Magnetic resonance imaging, a noninvasive nuclear procedure for imaging tissues of high fat and water content that cannot be seen with other radiologic techniques.

Pituitary gland—The master gland located in the middle of the head that controls the endocrine glands and affects most bodily functions.

Prostaglandins—A group of nine naturally occurring chemicals in the body that affect smooth muscles.

Serous—Thin and watery, like serum.

only one organ affected, steroids may be injected locally, or a drug called indomethacin may be used. Indomethacin is an anti-inflammatory medication that may achieve a similar response with less severe side effects.

The disease fluctuates markedly. If only one system is involved, the disease often resolves by itself. Multisystem disease usually needs treatment although it may disappear spontaneously. The disease is not normally fatal unless organs vital to life are damaged. In general, the younger the child at diagnosis and the more organs involved, the poorer the outlook. If the condition resolves, there could still be long-term complications because of the damage done while the disease was active.

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ORGANIZATIONS

Histiocytosis Association of America. 302 North Broadway, Pitman, NJ 08071. 800–548–2758 (USA and Canada). <http://www.histio.org>.

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Hodgkin's disease

Definition

Hodgkin's disease is a rare **lymphoma**, a cancer of the lymphatic system.

Description

Hodgkin's disease, or Hodgkin's lymphoma, was first described in 1832 by Thomas Hodgkin, a British physician. Hodgkin clearly differentiated between this disease and the much more common **non-Hodgkin's lymphomas**. Prior to 1970, few individuals survived Hodgkin's disease. Now, however, the majority of individuals with this cancer can be cured.

The lymphatic system

The lymphatic system is part of the body's immune system, for fighting disease, and a part of the blood-producing system. It includes the lymph vessels and nodes, and the spleen, bone marrow, and thymus. The narrow lymphatic vessels carry lymphatic fluid from throughout the body. The lymph nodes are small organs that filter the lymphatic fluid and trap foreign substances, including viruses, bacteria, and cancer cells. The spleen, in the upper left abdomen, removes old cells and debris from the blood. The bone marrow, the tissue inside the bones, produces new red and white blood cells.

Lymphocytes are white blood cells that recognize and destroy disease-causing organisms. Lymphocytes are produced in the lymph nodes, spleen, and bone marrow. They circulate throughout the body in the blood and lymphatic fluid. Clusters of immune cells also exist in major organs.

Hodgkin's lymphoma

Hodgkin's disease is a type of lymphoma in which antibody-producing cells of the lymphatic system begin to grow abnormally. It usually begins in a lymph node and progresses slowly, in a fairly predictable way, spreading via the lymphatic vessels from one group of lymph nodes to the next. Sometimes it invades organs that are adjacent to the lymph nodes. If the cancer cells spread to the blood, the disease can reach almost any site in the body. Advanced cases of Hodgkin's disease may involve the spleen, liver, bone marrow, and lungs.

There are different subtypes of Hodgkin's disease:

- nodular sclerosis (30–60% of cases)
- mixed cellularity (20–40% of cases)
- lymphocyte predominant (5–10% of cases)
- lymphocyte depleted (less than 5% of cases)
- unclassified

Demographics

The American Cancer Society estimates that there will be 7,400 new cases of Hodgkin's disease in the United States in 2001—3,500 in females and 3,900 in males. It is estimated that 700 men and 600 women in the United States will die of the disease in 2001.

Hodgkin's disease can occur at any age. However, the majority of cases develop in early adulthood (ages 15–40) and late adulthood (after age 55). Approximately 10–15% of cases are in children under age 17. It is more common in boys than in girls under the age of 10. The disease is very rare in children under five.

Causes and symptoms

The cause of Hodgkin's disease is not known. It is suspected that some interaction between an individual's genetic makeup, environmental exposures, and infectious agents may be responsible. Immune system deficiencies also may be involved.

Early symptoms of Hodgkin's disease may be similar to those of the flu:

- fevers, **night sweats**, chills
- **fatigue**
- loss of appetite (anorexia)
- weight loss
- itching
- pain after drinking alcoholic beverages
- swelling of one or more lymph nodes

Sudden or emergency symptoms of Hodgkin's disease include:

- sudden high fever
- loss of bladder and/or bowel control
- numbness in the arms and legs and a loss of strength

As lymph nodes swell, they may push on other structures, causing a variety of symptoms:

- pain due to pressure on nerve roots
- loss of function in muscle groups served by compressed nerves
- coughing or shortness of breath due to compression of the windpipe and/or airways, by swollen lymph nodes in the chest
- kidney failure from compression of the ureters, the tubes that carry urine from the kidneys to the bladder
- swelling in the face, neck, or legs, due to pressure on veins
- paralysis in the legs due to pressure on the spinal cord

As Hodgkin's disease progresses, the immune system becomes less effective at fighting infection. Thus, patients with Hodgkin's lymphoma become more susceptible to both common infections caused by bacteria and unusual (opportunistic) infections. Later symptoms of Hodgkin's disease include the formation of tumors.

Significantly, as many as 75% of individuals with Hodgkin's disease do not have any typical symptoms.

Diagnosis

As with many forms of cancer, diagnosis of Hodgkin's disease has two major components.

- identification of Hodgkin's lymphoma as the cause of the patient's disease
- staging of the disease to determine how far the cancer has spread

The initial diagnosis of Hodgkin's disease often results from abnormalities in a chest **x ray** that was performed because of nonspecific symptoms. The physician then takes a medical history to check for the presence of symptoms and conducts a complete physical examination.

Lymph node biopsy

The size, tenderness, firmness, and location of swollen lymph nodes are determined and correlated with any signs of infection. In particular, lymph nodes that do not shrink after treatment with **antibiotics** may be a cause for concern. The lymph nodes that are most often affected by Hodgkin's disease include those of the neck, above the collarbone, under the arms, and in the chest above the diaphragm.

Diagnosis of Hodgkin's disease requires either the removal of an entire enlarged lymph node (an excisional **biopsy**) or an incisional biopsy, in which only a small part of a large tumor is removed. If the node is near the skin, the biopsy is performed with a local anesthetic. However, if it is inside the chest or abdomen, general anesthesia is required.

The sample of biopsied tissue is examined under a microscope. Giant cells called Reed-Sternberg cells must be present to confirm a diagnosis of Hodgkin's disease. These cells, which usually contain two or more nuclei, are named for the two pathologists who discovered them. Normal cells have only one nucleus (the organelle within the cell that contains the genetic material). Affected lymph nodes may contain only a few Reed-Sternberg cells and they may be difficult to recognize. Characteristics of other types of cells in the biopsied tissue help to diagnose the subtype of Hodgkin's disease.

A fine needle aspiration (FNA) biopsy, in which a thin needle and syringe are used to remove a small amount of fluid and bits of tissue from a tumor, has the advantage of not requiring surgery. An FNA may be performed prior to an excisional or incisional biopsy, to check for infection or for the spread of cancer from another organ. However an FNA biopsy does not provide enough tissue to diagnose Hodgkin's disease.

Occasionally, additional biopsies are required to diagnose Hodgkin's disease. In rare instances, other tests, that detect certain substances on the surfaces of cancer cells or changes in the DNA of cells, are used to distinguish Hodgkin's disease from non-Hodgkin's lymphoma.

Clinical staging

Staging is very important in Hodgkin's disease. This is because the cancer usually spreads in a predictable pattern, without skipping sets of lymph nodes until late in the progression of the disease.

IMAGING Imaging of the abdomen, chest, and pelvis is used to identify areas of enlarged lymph nodes and abnormalities in the spleen or other organs. Computed tomography (CT or CAT) scans use a rotating x-ray beam to obtain pictures. **Magnetic resonance imaging** (MRI) uses magnetic fields and radio waves to produce images of the body. Chest x rays also may be taken. These images will reveal rounded lumps called nodules in the affected lymph nodes and other organs.

Another imaging technique for Hodgkin's disease is a **gallium scan**, in which the radioactive element gallium is injected into a vein. The cancer cells take up the gallium and a special camera that detects the gallium is used to determine the location and size of tumors. Gallium scans are used when Hodgkin's disease is in the chest and may be hard to detect by other methods. Gallium scans also are used to monitor progress during treatment.

A lymphangiogram, a radiograph of the lymphatic vessels, involves injecting a dye into a lymphatic vessel in the foot. Tracking of the dye locates the disease in the abdomen and pelvis. This method is used less frequently and is usually not used with children.

Positron emission tomography (PET) scans are an extremely accurate method for staging Hodgkin's disease. A very low dose of radioactive glucose, a sugar, is injected into the body. The glucose travels to metabolically active sites, including cancerous regions that require large amounts of glucose. The PET scan detects the radioactivity and produces images of the entire body that distinguish between cancerous and non-cancerous tissues.

BONE MARROW **Anemia** (a low red-blood-cell count), fevers, or night sweats are indications that Hodgkin's disease may be in the bone marrow. In these cases, a bone marrow aspiration and biopsy may be ordered. In biopsy, a large needle is used to remove a narrow, cylindrical piece of bone. Alternatively, an aspiration, in which a needle is used to remove small bits of bone marrow, may be used. The marrow usually is removed from the back of the hip or other large bone. This procedure may help to determine cancer spread.

Pathological staging

Sometimes further staging, called pathological staging or a staging laparotomy, is used for Hodgkin's disease. In this operation, a surgeon checks the abdominal

lymph nodes and other organs for cancer and removes small pieces of tissue. A pathologist examines the tissue samples for Hodgkin's disease cells. Usually the spleen is removed (a **splenectomy**) during the laparotomy. The splenectomy helps with staging Hodgkin's disease, as well as removing a disease site.

Treatment team

The cancer care team for Hodgkin's disease includes a medical oncologist (a physician specializing in cancer), oncology nurses, technicians, and social workers. A surgeon performs the biopsies, as well as the laparotomy and splenectomy if required. Pathologists examine the biopsy specimens for the presence of Reed-Sternberg and other abnormal cells.

In the United States, most children with Hodgkin's disease are treated at children's cancer centers. Here, the treatment team includes psychologists, child life specialists, nutritionists, and educators, as well as a pediatric oncologist.

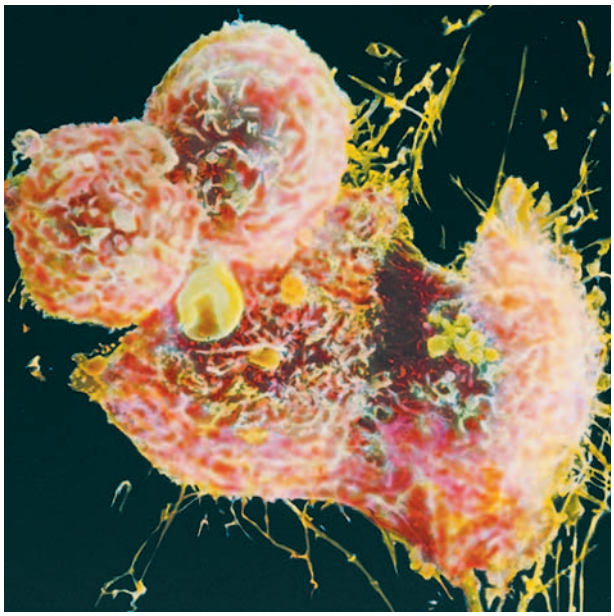
Clinical staging, treatments, and prognosis

The stages

All of the available treatments for Hodgkin's disease have serious side effects, both short and long-term. However, with accurate staging, physicians and patients often can choose the minimum treatment that will cure the disease. The staging system for Hodgkin's disease is the Ann Arbor Staging Classification, also called the Cotswold System or the Revised Ann Arbor System.

Hodgkin's disease is divided into four stages, with additional substages:

- Stage I: The disease is confined to one lymph node area
- Stage IE: The disease extends from the one lymph node area to adjacent regions
- Stage II: The disease is in two or more lymph node areas on one side of the diaphragm (the muscle below the lungs)
- Stage IIE: The disease extends to adjacent regions of at least one of these nodes
- Stage III: The disease is in lymph node areas on both sides of the diaphragm
- Stage IIIE/IIISE: The disease extends into adjacent areas or organs (IIIE) and/or the spleen (IIISE)
- Stage IV: The disease has spread from the lymphatic system to one or more other organs, such as the bone marrow or liver



A scanning electron micrograph (SEM) image of dividing Hodgkin's cells from the pleural effusions (abnormal accumulations of fluid in the lungs) of a 55-year-old male patient. *(Photograph by Dr. Andrejs Liepins, National Audubon Society Collection/Photo Researchers, Inc. Reproduced by permission.)*

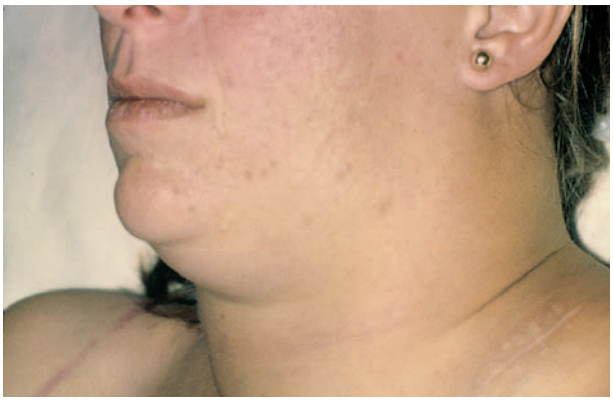
Treatment for Hodgkin's disease depends both on the stage of the disease and whether or not symptoms are present. Stages are labeled with an A if no symptoms are present. If symptoms are present, the stage is labeled with a B. These symptoms include:

- loss of more than 10% of body weight over the previous six months
- fevers above 100 degrees F
- drenching night sweats

Treatments

RADIATION THERAPY **Radiation therapy** and/or **chemotherapy** (drug therapy) are the standard treatments for Hodgkin's disease. If the disease is confined to one area of the body, radiotherapy is usually used. This treatment, with x rays or other high-energy rays, also is used when the disease is in bulky areas such as the chest, where chemotherapeutic drugs cannot reach all of the cancer. External-beam radiation, a focused beam from an external machine, is used to irradiate only the affected lymph nodes. This procedure is called involved field radiation.

More advanced stages of Hodgkin's disease may be treated with mantle field radiation, in which the lymph nodes of the neck, chest, and underarms are irradiated. Inverted Y field radiation is used to irradiate the spleen



Swollen lymph nodes of a Hodgkin's disease patient. *(Custom Medical Stock Photo. Reproduced by permission.)*

and the lymph nodes in the upper abdomen and pelvis. Total nodal irradiation includes both mantle field and inverted Y field radiation.

Since external-beam radiation damages healthy tissue near the cancer cells, the temporary side effects of radiotherapy can include sunburn-like skin damage, fatigue, nausea, and **diarrhea**. Other temporary side effects may include a sore throat and difficulty swallowing. Long-term side effects depend on the dose and the location of the radiation and the age of the patient. Since radiation of the ovaries causes permanent sterility (the inability to have offspring), the ovaries of girls and young women are protected during radiotherapy. Sometimes the ovaries are surgically moved from the region to be irradiated.

CHEMOTHERAPY If the Hodgkin's disease has progressed to additional lymph nodes or other organs, or if there is a recurrence of the disease within two years of radiation treatment, chemotherapy is used.

Chemotherapy utilizes a combination of drugs, each of which kills cancer cells in a different way. The most common chemotherapy regimens for Hodgkin's disease are MOPP (either **mechlorethamine** or **methotrexate** with Oncovin, **procarbazine**, prednisone) and ABVD (Adriamycin or **doxorubicin**, **bleomycin**, **vincristine**, **dacarbazine**). Each of these consists of four different drugs. ABVD is used more frequently than MOPP because it has fewer severe side effects. However MOPP is used for individuals who are at risk for heart failure. The chemotherapeutic drugs may be injected into a vein or muscle, or taken orally, as a pill or liquid.

Children who are sexually mature when they develop Hodgkin's disease, and whose muscle and bone mass are almost completely developed, usually receive the same treatment as adults. Younger children usually are treated with chemotherapy, since radiation will adversely affect bone and muscle growth. However, radiation may be used in low dosages, in combination with chemotherapy. The chemotherapy for children with Hodgkin's disease usually includes more drugs than ABVD and MOPP.

The side effects of chemotherapy for Hodgkin's disease depend on the dose of drugs and the length of time they are taken. Since these drugs target rapidly dividing cancer cells, they also affect normal cells that grow rapidly. These include the cells of the bone marrow, the linings of the mouth and intestines, and hair follicles. Damage to bone marrow leads to lower white blood cell counts and lower resistance to infection. It also leads to lower red blood cell counts that can result in fatigue and easy bleeding and bruising. Damage to intestinal cells leads to a loss of appetite (anorexia), and nausea and vomiting. Mouth sores and hair loss (alopecia) also are common side effects of chemotherapy. These side effects disappear when the chemotherapy is discontinued. Some drugs can reduce or prevent the **nausea and vomiting**.

Chemotherapy for Hodgkin's disease may lead to long-term complications. The drugs may damage the heart, lungs, kidneys, and liver. In children, growth may be impeded. Some chemotherapy can cause sterility, so men may choose to have their sperm frozen prior to treatment. Women may stop ovulating and menstruating during chemotherapy. This may or may not be permanent.

Treatment for higher-stage Hodgkin's disease often involves a combination of radiotherapy and chemotherapy. Following three or four chemotherapy regimens, involved field radiation may be directed at the most affected areas of the body. The long-term side effects often are more severe when radiation and chemotherapy are used in combination.

The development of a second type of cancer is the most serious risk from radiation and chemotherapy treatment for Hodgkin's disease. In particular, there is a risk of developing leukemia, **breast cancer**, bone cancer, or **thyroid cancer**. Chemotherapy, particularly MOPP, or chemotherapy in conjunction with radiotherapy, significantly increases the risk for leukemia.

RESISTANT, PROGRESSIVE, AND RECURRENT HODGKIN'S DISEASE Following treatment, the original diagnostic tests for Hodgkin's disease are repeated, to determine whether all traces of the cancer have been eliminated and to check for long-term side effects of treatment. In resistant Hodgkin's disease, some cancer cells remain following treatment. If the cancer continues to spread during treatment, it is called progressive Hodgkin's disease. If the disease returns after treatment, it is known as recurrent Hodgkin's disease. It may recur in the area where it first started or elsewhere in the body. It may recur immediately after treatment or many years later.

KEY TERMS

Antibody—An immune system protein that recognizes a specific foreign molecule.

Biopsy—The removal of a small sample of tissue for examination under a microscope; used for the diagnosis of cancer and to check for infection.

Bone marrow—Tissue inside the bones that produce red and white blood cells.

Chemotherapy—Treatment with various combinations of chemicals or drugs, particularly for the treatment of cancer.

Epstein-Barr virus (EBV)—Very common virus that infects immune cells and can cause mononucleosis.

Interferon—A potent immune-defense protein produced by viral-infected cells; used as an anti-cancer and anti-viral drug.

Interleukins—A family of potent immune-defense molecules; used in various medical therapies.

Laparotomy—A surgical incision of the abdomen.

Leukapheresis—A technique that uses a machine to remove stem cells from the blood; the cells are frozen and then returned to the patient following treatment that has destroyed the bone marrow.

Lymph nodes—Small round glands, located throughout the body and containing lymphocytes that remove foreign organisms and debris from the lymphatic fluid.

Lymphatic system—The vessels, lymph nodes, and organs, including the bone marrow, spleen, and thymus, that produce and carry white blood cells to fight disease.

Lymphocyte—White blood cells that produce antibodies and other agents for fighting disease.

PBSCT—Peripheral blood stem cell transplant; a method for replacing blood-forming cells that are destroyed by cancer treatment.

Radiotherapy—Disease treatment involving exposure to x rays or other types of radiation.

Reed-Sternberg cells—An abnormal lymphocyte that is characteristic of Hodgkin's disease.

Spleen—An organ of the lymphatic system, on the left side of the abdomen near the stomach; it produces and stores lymphocytes, filters the blood, and destroys old blood cells.

Splenectomy—Surgical removal of the spleen.

Staging—The use of various diagnostic methods to accurately determine the extent of disease; used to select the appropriate type and amount of treatment and to predict the outcome of treatment.

Stem cells—The cells from which all blood cells are derived.

Thymus—An organ of the lymphatic system, located behind the breast bone, that produces the T lymphocytes of the immune system.

Thyroid—A gland in the throat that produces hormones that regulate growth and metabolism.

Additional treatment is necessary with these types of Hodgkin's disease. If the initial treatment was radiation therapy alone, chemotherapy may be used, or vice versa. Chemotherapy with different drugs, or higher doses, may be used to treat recurrent Hodgkin's. However, radiation to the same area is never repeated.

BONE MARROW AND PERIPHERAL BLOOD STEM CELL TRANSPLANTATIONS An autologous bone marrow and/or a peripheral blood stem cell transplantation (PBSCT) often is recommended for treating resistant or recurrent Hodgkin's disease, particularly if the disease recurs within a few months of a chemotherapy-induced remission. These transplants are autologous because they utilize the individual's own cells. The patient's bone marrow cells or peripheral blood stem cells (immature bone marrow cells found in the blood) are collected and frozen prior to high-dosage chemotherapy, which destroys bone marrow cells. A procedure called leukapheresis is used to collect the stem cells. Following the high-dosage chemotherapy, and possibly radiation, the bone marrow cells or stem cells are reinjected into the individual.

Alternative and complementary therapies

Most complementary therapies for Hodgkin's disease are designed to stimulate the immune system to destroy cancer cells and repair normal cells that have been damaged by treatment. These therapies are used in conjunction with standard treatment.

Immunologic therapies, also known as immunotherapies, biological therapies, or biological response modifier therapies, utilize substances that are produced by the immune system. These include interferon (an immune system protein), **monoclonal antibodies**

(specially engineered antibodies), colony-stimulating (growth) factors (such as **filgrastim**), and **vaccines**. Many immunotherapies for Hodgkin's disease are experimental and available only through **clinical trials**. These biological agents may have side effects.

Coenzyme Q10 (CoQ10) and polysaccharide K (PSK) are being evaluated for their ability to stimulate the immune system and protect healthy tissue, as well as possible anti-cancer activities. Camphor, also known as 714-X, green tea, and hoxsey (which is a mixture of a number of substances), have been promoted as immune system enhancers. However there is no evidence that they are effective against Hodgkin's disease. Hoxsey, in particular, can produce serious side effects.

Prognosis

Hodgkin's disease, particularly in children, is one of the most curable forms of cancer. Approximately 90% of individuals are cured of the disease with chemotherapy and/or radiation.

The one-year relative survival rate following treatment for Hodgkin's disease is 93%. Relative survival rates do not include individuals who die of causes other than Hodgkin's disease. The percentage of individuals who have not died of Hodgkin's disease within five years of diagnosis is 90–95% for those with stage I or stage II disease. The figure is 85–90% for those diagnosed with stage III Hodgkin's and approximately 80% for those diagnosed with stage IV disease. The 15-year relative survival rate is 63%. Approximately 75% of children are alive and cancer free 20 years after the original diagnosis of Hodgkin's.

Acute myelocytic leukemia, a very serious cancer, may develop in as many as 2–6% of individuals receiving certain types of treatment for Hodgkin's disease. Women under the age of 30 who are treated with radiation to the chest have a much higher risk for developing breast cancer. Both men and women are at higher risk for developing lung or thyroid cancers as a result of chest irradiation.

Individuals with the type of Hodgkin's disease known as nodular lymphocytic predominance have a 2% chance of developing non-Hodgkin's lymphoma. Apparently, this is a result of the Hodgkin's disease itself and not the treatment.

Coping with cancer treatment

Sufficient rest and good nutrition are important for relieving the side effects of treatment for Hodgkin's disease. As strength returns, a weekly exercise routine should be initiated. Support groups can be beneficial for helping with emotional problems that may arise during treatment.

QUESTIONS TO ASK THE DOCTOR

- What type of Hodgkin's disease do I have?
- What is the stage of my disease?
- What are the choices for treatment and what do you recommend?
- Should I obtain a second opinion?
- What are the short-term side effects of the treatment and what can be done about them?
- What are the possible long-term side effects of the treatment?
- Are there other risks from the treatment?
- How should I prepare for the treatment?
- How long will the treatment continue?
- What is the recovery time following the treatment?
- What are the chances of success?
- Are there clinical trials which may be appropriate for me?
- Are there complementary or alternative therapies that may be helpful?
- What is the likelihood that the cancer will return? How will a recurrence be diagnosed?
- Is a recurrence more likely with one treatment than with another?

Clinical trials

At least 115 clinical trials for the treatment of Hodgkin's disease were recruiting or planning to recruit participants. A number of these studies are directed at treating resistant (refractory) or recurrent (relapsed) Hodgkin's disease in both children and adults. Some are aimed at specific stages or subtypes of Hodgkin's disease. Some trials are for previously treated individuals and others are for those who have not yet received treatment.

Clinical trials of new treatments for Hodgkin's disease include:

- new drugs
- new chemotherapies
- monoclonal antibody therapy
- interferon, interleukin-2, and interleukin-12
- a vaccine made from cancer cells that contain the **Epstein-Barr virus**

- bone marrow and umbilical cord blood transplantations
- PBSCT
- various combinations of treatments

There also are ongoing genetic studies of children and adults with Hodgkin's disease and quality-of-life studies of children who are undergoing treatment.

Prevention

There are very few known risk factors for Hodgkin's disease. A family history of the disease and the presence of the Epstein-Barr virus are associated with an increased risk. Individuals with acquired immunodeficiency syndrome (AIDS) are particularly susceptible to Hodgkin's disease.

Special concerns

Follow-up examinations continue for many years following treatment for Hodgkin's disease. Women who have had chest irradiation must have frequent mammograms and clinical and breast self examinations for early detection of breast cancer. Frequent physical exams and chest x rays may help to detect lung or thyroid cancer. Treatment with mantle field radiation causes hyperthyroidism, which requires thyroid medication and annual thyroid function tests.

Individuals with Hodgkin's disease do not have normal immune system function, a problem that can be intensified by chemotherapy, radiation, and removal of the spleen. Therefore, vaccinations and prompt treatment of infections are very important.

See also Amenorrhea; Bone marrow transplantation; Childhood cancers.

Resources

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ORGANIZATIONS

American Cancer Society. (800) ACS-2345. <http://www.cancer.org>. Provides information, funds for cancer research, prevention programs, and patient services, including education and support programs for patients and families, temporary accommodations for patients, and camps for children with cancer.

ClinicalTrials.gov. U. S. National Library of Medicine. National Institutes of Health. 8600 Rockville Pike, Bethesda, MD 20894. <http://clinicaltrials.gov/ct/gui/c/a1b/screen/BrowseAny/action/GetStudy?JServSessionIdcs_current=mgdpq4z7pm>. Information about clinical trials involving Hodgkin's disease.

Cure for Lymphoma Foundation. 215 Lexington Avenue, New York, NY 10016. (212) 213-9595. (800)-CFL-6848. infocfl@cfl.org. <http://www.cfl.org/home.html>. An advocacy organization that provides education and support programs, research grants, and information on clinical trials for Hodgkin's and non-Hodgkin's lymphomas.

The Leukemia and Lymphoma Society. 600 Third Avenue, New York, NY 10016. (800) 955-4572. (914) 949-5213. <http://www.leukemia-lymphoma.org> Provides information, support, and guidance to patients and health care professionals.

The Lymphoma Research Foundation of America, Inc. 8800 Venice Boulevard, Suite 207, Los Angeles, CA 90034. (310) 204-7040). <http://www.lymphoma.org>. Supports research into treatments for lymphoma and provides educational and emotional support programs for patients and families.

National Cancer Institute. Public Inquiries Office, Building 31, Room 10A31, 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (800)-4-CANCER. <http://www.nci.nih.gov/>. <http://cancernet.nci.nih.gov>. Provides information on cancer and on clinical trials; conducts cancer research.

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Home health services

Definition

Home health services refers to those health care services provided to the patient in his or her own home.

Description

Home health services can vary depending on the insurance coverage, but usually include nursing, physical therapy, occupational therapy, speech therapy, home health aides, social work, nutritional education, infusion therapy, blood drawing, and other laboratory services. Such services may also include bringing medical equipment into the home for patient use. Home health services do not provide around-the-clock care, but rely on the patient having other caregivers, such as family members, friends, or other community resources.

Home care services can be provided by many different organizations, such as the Visiting Nurses Association (VNA), home health agencies (which vary in the range of services provided), hospice organizations, providers of home medical equipment, and pharmacies with delivery services. Patients requiring a range of specialized services may find more continuity of care if one agency is able to provide all, or almost all, of the services they need. **Hospice care** is care provided to patients who are terminally ill. Most hospices care for their clients within the home. The goal of hospice is to help the client and their family deal with the physical, emotional, and spiritual issues associated with dying. Excellent pain management is a priority.

Nursing care

Skilled nursing care provides the backbone for home care. Visits may include wound and ostomy care; infusion therapy such as home **chemotherapy**, **antibiotics**, or home parenteral nutrition (HPN); patient and caregiver teaching; ongoing assessment of the client's physical and emotional condition and progress; pain control; psychological support; and supervision of home health aides. The nurse may function as a case manager and coordinate the various other services the client is receiving. The nurse assesses the home environment for safety and for appropriateness of continued home care.

Physical therapy

Physical therapists develop a plan for the client to restore (as much as possible) the physical condition lost following surgery or as a result of a decline due to the disease process. They also teach patients how to prevent further injury or deterioration and how to maintain gains made.

A home healthcare nurses tends to a patient. *(Reproduced by permission.)*

Occupational therapy

Occupational therapists assist patients in restoring or enhancing their ability to perform their tasks of daily living. Patients may need to learn how to use adaptive equipment such as a prosthesis. The goal is to achieve the highest level of functioning possible.

Speech therapy

Speech therapists work with clients who have difficulty swallowing or clearly communicating.

Home health aides

Home health aides function under the supervision of a registered nurse. They provide care with personal hygiene, such as bathing and dressing, feeding, and ambulating. They may assist a nurse in providing patient care. They may provide homemaking services and companionship, or those tasks may be covered by a homemaker or attendant.

Social work

Social workers may assist clients in accessing the services that are available to them based on their insurance, and in learning what community resources exist. They may also facilitate the referral process, and provide counseling and patient advocacy.

Nutritional education

Nutritionists and registered dieticians may educate clients on their nutritional needs, and on how to go about attaining them. They may also be involved if HPN is required.

Infusion therapy

Some patients may receive their chemotherapy or antibiotics at home, or may require infusion of liquid

nutrition (HPN). While these services may be provided by a nurse, a separate agency or company may provide the equipment and products.

Laboratory work

Blood drawing and other laboratory services may be provided by a nurse, a phlebotomist, or a laboratory technician.

Home medical equipment

Following surgery or treatment in a hospital, patients may need the delivery and servicing of items such as special beds, wheelchairs, walkers, catheters, and wound care and ostomy supplies.

Volunteers

Volunteers may provide a range of assistance such as respite care for the primary caregiver(s), caring for the home, cooking, cleaning, emotional support, companionship, running errands, making telephone calls, child care, elder care, and providing transportation. They may come from the patient's circle of friends or religious organization, or from such agencies as Meals on Wheels.

Causes

Many individuals with conditions that do not necessitate care in a hospital setting often require short-term or long-term home care. They may need care to assist them in regaining their health similar to that prior to their illness, or may need ongoing care as their condition deteriorates due to metastatic disease. One trend that is gathering speed in the early 2000s is an increase in home health care services as opposed to nursing home care.

Special concerns

Insurance coverage plays a major role in funding home health care. In organizing home care the patient must fully understand which services will be fully covered, covered but with a co-payment, or not covered at all. Insurance coverage may vary depending on whether the service provider is within a specified approved network. It must also be clear how often and for how long the services will be needed, and whether the insurance benefits cover the entire time period of anticipated care. The patient's safety must always remain a priority. The patient and the caregiver(s) may suffer from isolation and **depression**. Primary caregivers may become overwhelmed with caring for the patient, and there may come a point at which the level of care needed may no longer be able to be provided in the home setting. The health of the primary caregiver must periodically be assessed.

KEY TERMS

Home parenteral nutrition (HPN)—HPN provides liquid nutrition via infusion for patients who are malnourished, or who have had surgery altering the usual process of chewing, swallowing, or digesting food.

Meditation—Meditation is a technique in which the individual focuses on a word or phrase to the exclusion of other thoughts. It has been shown to lower blood pressure and reduce stress.

Respite care—A form of temporary home health care that allows family members some time away from patient care. Respite care is usually short-term, ranging from a few hours to a weekend.

T'ai chi—An Asian practice of breathing and slow physical movements that develops strength and reduces stress.

Telehealth—The use of the telephone, Internet, and other forms of telecommunication to support long-distance health care, education of health care professionals, and public health concerns.

Treatments

Treatments provided in the home include wound and ostomy care, intravenous (IV) chemotherapy or antibiotics, HPN, and physical, occupational, and speech therapy.

Newer trends and future concerns

One trend in home health care is greater use of the telephone and Internet for contact between home health care workers and medical professionals, and for information gathering. The U. S. Department of Health and Human Services has sponsored a new web site intended to help consumers as well as professionals make informed choices about home health care agencies. In addition, the growth of so-called telehealth systems has already had an impact on nursing education and practice in the home health care field. The field of telehealth is expected to expand dramatically in the early 2000s, as experts estimate that home health care is 10–15 years behind other fields in its use of computers.

Another trend is the growing emphasis on culturally sensitive home health care. In many cases, patients from minority ethnic groups and cultures are more comfortable being cared for in their homes by caregivers who share their background or have been trained to

QUESTIONS TO ASK THE DOCTOR

- What kind of home care will I need?
- For how long will I need the different services?
- What happens if my condition worsens?
- Will my insurance cover the services you are prescribing?
- What kind of care is available to help my family care for me?
- Are there alternative therapies that would help my condition?
- Are any of these therapies covered by my insurance?
- Are there any side effects to these therapies?
- Who is in charge of making sure my pain is well controlled?

understand it than to be sent to large urban nursing homes where they are isolated from familiar customs and language. Studies of the feasibility of home health care for Native Americans in remote locations are presently being conducted in Canada.

One worrisome concern for the future is the increasing difficulty of recruiting and retaining high-quality home health care workers in the United States and Canada. The aging of the general North American population coupled with the high turnover in the field of home health care poses a serious problem for policy makers.

Alternative and complementary therapies

Clients may contract to have home acupuncture or massage therapy. On their own they may engage in yoga, t'ai chi, meditation, guided imagery, visualization, or other stress-reducing techniques that help them better cope with their situation. They may also choose to investigate herbal supplements and medications; all supplemental medications should be approved by a physician before use.

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National Center for Complementary and Alternative Medicine. NCCAM Clearinghouse, P.O. Box 8218, Silver Spring, MD 20907–8218. 888–644–6226. <http://nccam.nih.gov>.

Office for the Advancement of Telehealth. 5600 Fishers Lane, Room 7C-22, Rockville, MD 20857. (301) 443-0447. Fax: (301) 443-1330. <http://telehealth.hrsa.gov>.

Visiting Nurse Association of America. 11 Beacon Street, Suite 910; Boston, MA 02108. 617–523–4042. Fax: 617–227–4843. <http://www.vnaa.org>.

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Horner's syndrome

Description

William Edmonds Horner (1793–1853) first described a small muscle at the angle of the eyelid (tensor tarsi) as well as a description of an ingenious

operation to correct problems with the lower lid in 1824 in the American Journal of the Medical Sciences. Since that time, his name has been associated with the syndrome of a small, regular pupil, drooping of the eyelid on the same side and occasional loss of sweat formation on the forehead of the affected eye. In appearance, it occurs on one side of the face with a sinking in of the eyeball (enophthalmos), drooping upper eyelid (ptosis), slight elevation of the lower lid, excessive contraction of the pupil of the eye (miosis), narrowing of the eyelid, and an absence of facial sweat on the affected side (anhidrosis). Other symptoms may include a variation in eye color of the iris and changes in the consistency of tears.

Causes

Horner's syndrome is caused by damage or interruption of the sympathetic nerve to the eye. There are two major divisions of the nervous system: the voluntary (conscious control) and involuntary (without conscious control). The involuntary (autonomic nervous system) has two divisions: sympathetic and parasympathetic nervous systems. Under normal conditions, there is a fine balance between sympathetic and parasympathetic stimulation. If an individual is threatened by a situation, the pupils dilate, blood is shifted to the muscles and the heart beats faster as the person prepares to fight or flee. This is sympathetic stimulation. The eye has both sympathetic (responds to challenges) and parasympathetic (slows the body down) innervation. The nerve that carries the sympathetic innervation travels down the spinal cord from the brain (hypothalamus), emerges in the chest cavity, and then finds it way up the neck along with the carotid artery and jugular vein through the middle ear and into the eye. If these sympathetic impulses were blocked, the eye would have an overbalance of parasympathetic supply, which would result in a constriction of the pupil, relaxation of all the muscles around the eye and a sinking of the eye into the orbit—Horner's syndrome. Thus, damage that occurs anywhere along the course of this nerve's route from the brain to the eye can evoke this syndrome.

If the syndrome exists from birth (congenital), it is typically noted around the age of two years with the presence of a variation in the color of the iris and the lack of a crease in the drooping eye. Since eye color is completed by the age of two, a variation in color is an uncommon finding in Horner's syndrome acquired later in life.

The common causes of acquired Horner's syndrome include aortic dissection (a tear in the wall of the aorta to create a false channel where blood becomes trapped), carotid dissection, tuberculosis, Pancoast tumor (a tumor in the upper end of the lung), brain tumors, spinal cord injury in the neck, trauma to the cervical or thoracic portions of the spinal cord, cluster migraine headache, vertebrae destruction or collapse, compression of the spinal cord by enlarged lymph nodes, and neck or thyroid surgery.

The diagnosis and localization of this disorder is made with the use of pharmacological testing by an ophthalmologist. The physician places drops of a 10% liquid cocaine into the eyes, blocking the parasympathetic nerves so the sympathetic nervous system can be evaluated. After thirty minutes, the dilation of the pupils is noted and a Horner's pupil dilates poorly. A positive cocaine test does not, however, localize the area of the damage. After waiting for 48 hours, other medications are used to determine where the nerve interruption occurs. This solution routinely has been hydroxyamphetamine bromide. However, it has not been routinely available and in 2004, a study reported that a phenylephrine solution works as well. An individual's urine can test positive for cocaine up to two days following the initial test.

Treatments

Treatment for congenital cases

Children who are diagnosed with Horner's syndrome of a congenital origin may undergo surgical correction to strengthen the muscle of the eyelid and give it an appearance similar to the unaffected eye. The surgery improves the appearance of the child but does not alleviate the syndrome. For these cases a plastic surgeon may be preferred. Occasionally Horner's syndrome may be seen in a newborn with a **neuroblastoma** (tumor originating from nerve cells). This is almost always a sign of a localized tumor and is associated with a relatively good prognosis. In these cases, a neurologist may be consulted for treatment since their specialty is the nervous system.

Treatment for acquired cases

The treatment for acquired Horner's syndrome depends upon the cause and is focused toward eliminating the disease that produces the syndrome. Frequently, there is no treatment that improves or reverses the condition, but recognition of the signs and symptoms is extremely important for early diagnosis and treatment. Early detection of the syndrome may facilitate treatment related to those caused by tumors as they can be removed before extensive damage is done. Causes related to an interruption in nerve transmission once the nerve leaves the spinal cord are usually related to blood circulation and are easier to treat. Any numbness or paralysis on one side of the body means the problem is within the spinal cord or brain and is more difficult to treat. Some acquired Horner's may be corrected slightly by plastic surgery for appearance changes.

KEY TERMS

Congenital—Present at and existing from the time of birth.

Hypothalamus—That part of the third ventricle in the brain which anatomically contains the optic nerves.

Neuroblastoma—A tumor of nervous system origin composed chiefly of neruoblasts (embryonic nerve cells), affecting mostly infants and children up to 10 years of age, usually arising in the autonomic nervous system.

Pancoast tumor—A tumor or growth in the pointed end of the lung.

Alternative and complementary therapies

Acupuncture may be utilized to enhance disruptions in nerve transmissions and herbs or supplements that improve circulation may benefit some cases of acquired syndrome. These herbs and supplements would include Gingko biloba and vitamin E. As with any complementary treatment, patients should notify their physician of any herbal or over-the-counter medications they are taking.

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Hospice care

Definition

Hospice care is palliative care given to individuals who are terminally ill with an expected survival of six months or less. The focus of hospice care is on meeting the physical, emotional, and spiritual needs of the dying individual, while fostering the highest quality of life possible.

Description

Hospice services provide palliative care to individuals with a life expectancy of six months or less. Most hospice care is provided in the home, but may take place in a hospice home or a hospice/palliative care area within a medical facility. Requesting hospice care may be the first time that individuals, or their families, acknowledge that their condition is not treatable. It may be the first time that they have to deal with their death as a reality taking place within a few months. The emotional journey to be able to deal with these issues may take a while, and therefore may delay the time when the person begins to receive hospice care.

The focus of hospice is not on treatment, but on pain and symptom management, comfort measures, acknowledging that the individual will die, supporting the family, and trying to provide the best quality of life for the time remaining. Hospice functions under the philosophy that although some terminally ill patients may no longer receive treatment, they still require and deserve care.

Hospice care is interdisciplinary in nature, providing the services of physicians, nurses, social workers, physical, speech, or occupational therapists, clergy or other spiritual guides, health care aides, and volunteers. Home hospice care relies on the family and friends of the patient to provide most of the daily care. Nursing and other services are provided daily or weekly, but with 24 hours, 7 days a week on-call access. Addressing the spiritual needs of the hospice client is a fundamental aspect of hospice care.

Some studies about hospice care have gleaned the following:

- When asked their preference, about two-thirds of cancer patients said they preferred to die in their own home.
- The majority of patients still die in the hospital.
- When surveyed, about 95% of families who received hospice care said that it had been helpful.
- Although satisfied with hospice care, caregivers report the job of caregiving as having a negative impact on their own quality of life, and felt the job was burdensome.
- When compared to a control group of noncaregivers, caregivers had higher levels of **depression**, anxiety, anger, and health problems. Caregivers had a higher

rate of deteriorating health, social, and occupational functioning.

- Quality of life was influenced by the individual's spiritual well-being.
- Hospice patients expressed feelings of conflict between a hope for living, and "living in hope," being able to reconcile with others and coming to terms with death.
- Although hospice is focused on helping people in the last six months of their life, most hospice patients only receive about one month of hospice care prior to their death.
- Only 20% of physicians' prognoses about a patient's survival was accurate. Sixty-three percent were overly optimistic, and 17% were overly pessimistic. The more experience the physicians had, the better their accuracy of prognosis.

Causes

Hospice care was first established in the United States in 1974 in Branford, Connecticut. The Branford hospice was patterned on St. Christopher's Hospice in London, which was established by Dame Cicely Saunders in 1967. In 1969, the book *On Death and Dying*, by Dr. Elizabeth Kugler-Ross identified five stages that a terminally ill person goes through. In the book, Dr. Kubler-Ross addressed the importance of patients having a role in the decisions affecting the quality of their life and death. In 1972 she testified at the first U.S. Senate national hearing on dying with dignity.

Deciding on hospice care is a choice made by the terminally ill individual. To be eligible, one's physician needs to document that the individual's survival is expected to be six months or less. Should the patient recover, and the prognosis change, the relationship with hospice is terminated, but can be reestablished when needed at a later date. Not all patients will choose hospice. If only home hospice care is available, individuals who would be eligible may decide that hospice is not a good choice for them. Reasons for not choosing home hospice include:

- The patient lives alone, with little or no family support available.
- The patient has a need for 24-hour nursing care.
- The patient has family, but they are unable to provide the supportive care required.
- The patient is concerned about being a burden to the caregiver.
- The patient feels more secure in a hospital environment.

KEY TERMS

Meditation—Meditation is a technique in which the individual focuses on a word or phrase to the exclusion of other thoughts. It has been shown to reduce stress and anxiety.

Palliative care—Care focused on providing comfort, not cure.

Respite care—A form of temporary home health care that allows family members some time away from patient care. Respite care is usually short-term, ranging from a few hours to a weekend.

T'ai chi—An Asian practice of breathing and slow physical movements that develops strength and reduces stress.

Telehealth—The use of the telephone, Internet, and other forms of telecommunication to support long-distance health care, education of health care professionals, and public health concerns.

Special concerns

A study looking at the communication between physicians and their dying patients found these issues to be very important:

- Being honest and straightforward with patients.
- A willingness to talk about dying.
- Being sensitive when conveying bad news.
- Listening to patients.
- Encouraging patients to ask questions.
- Finding a balance between being honest without discouraging hope.

A *Journal of the American Medical Association* article found that patients at the end of their life expressed these issues as important:

- being mentally aware
- not being a burden
- having their funeral arrangements planned
- helping others
- coming to peace with God
- freedom from pain
- talking about the meaning of death
- Among nine issues, dying at home was rated the least important.

QUESTIONS TO ASK THE DOCTOR

- What do you think is my prognosis?
- What choices are there to manage my pain and other symptoms?
- What level of symptom management can I expect to receive?
- What types of care, conventional or alternative, would improve the quality of the time I have left?
- Will my insurance cover the care you suggest?
- If I choose hospice care, how will that affect my relationship with my doctors and treatment team?
- What kind of support is there for my family, both until I die and afterwards?

Because time is limited for patients in hospice, patients and their caregivers need to act swiftly on areas of dissatisfaction, such as quality of care being provided or insufficient symptom management.

Treatments

Curative treatments are not a part of hospice care. However, hospice places great importance on minimizing or alleviating pain and symptoms such as appetite loss (anorexia), **fatigue**, weakness, constipation, difficulty breathing, confusion, nausea, vomiting, cough, and dry or sore mouth. For many with advanced cancer, fatigue may be their worst symptom. Research has shown that a tailored exercise program can increase activity tolerance without increasing fatigue. In addition, patients reported an increase in quality of life and decreased anxiety. Patients who expressed the most fatigue showed the most decrease in fatigue with the exercise program. Many hospice patients have breakthrough pain in addition to their chronic pain. Research using an indwelling subcutaneous needle for pain control showed 88% pain control with this method when pain was not well controlled with oral medications. Chronic pain requires ongoing pain relief, such as might be handled with a pump or patch. Good pain control may mean waking the patient up at night for oral medication to prevent the pain from mounting during sleep.

Alternative and complementary therapies

Dealing with the issues of death may be addressed through talking with others, writing in a journal, creative expression such as painting, writing a poem, or composing music. Meditation may be beneficial to some patients. Gentle body movements such as with t'ai chi or yoga may be helpful, depending on the patient's activity tolerance.

Recent trends

A recent development in facilitating hospice care in the patient's home is night respite service. In general, respite care refers to home health care offered by volunteers or home health caregivers that allows the patient's family a few hours or a weekend away from direct patient care. Night respite care in a hospice setting involves trained aides who care for the patient in his or her home overnight, thus allowing other family members to catch up on necessary sleep. Studies indicate that many patients as well as family members feel that night respite care is a good option that allows patients to remain at home rather than being transferred to an inpatient hospice.

One trend in hospice care that has attracted considerable interest in the early 2000s is ethnically and culturally sensitive hospice care. As of 2004, hospice services in the United States and Canada are utilized disproportionately by Caucasians. One innovative Native American hospice program that is working well is a palliative care program at the Pueblo of Zuni in New Mexico. The Zuni program combines tribal-based home health care with inpatient care at an Indian Health Service (IHS) hospital.

Another significant trend in hospice care is the greater use of webcams, video phones, and other devices that have been introduced along with the computerization of hospital and hospice facilities. The rapid growth of "telehealth" since the mid-1990s indicates that technological innovations in telecommunications will affect hospice care as they have home health care and other outpatient settings.

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American Pain Society. 4700 W. Lake Ave., Glenview, IL 60025. 847-375-4715. <http://ampainsoc.org>.

Hospice Association of America. 228 Seventh Street, SE; Washington, DC 20003. 202-546-4759. Fax: 202-547-9559. <www.hospice-america.org>.

National Association for Home Care. 228 7th Street, S.E. Washington, D.C. 20003. 202-547-7424. <http://www.nahc.org>.

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Cancer Resources. 457 West 22nd Street, Suite B, New York, NY 10011. 800-401-2233. Fax: 212-243-1063. e-mail: info@cancerresources.com. <http://www.cancerresouces.com>.

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HPV *see* **Human papilloma virus**

Human growth factors

Definition

Human growth factors are compounds made by the body that function to regulate cell division and cell survival. Some growth factors are also produced in the laboratory by genetic engineering and are used in biological therapy.

Description

Human tumors express large amounts of growth factors and their receptors. A tumor will not grow beyond the size of a pinhead without new blood vessels to supply oxygen and nutrients. Growth factors are significant because they can induce angiogenesis, the formation of blood vessels around a tumor. These growth factors also encourage cell proliferation, differentiation, and migration on the surfaces of the endothelial cells—cells found inside the lining of blood vessels. Of the approximately 20 proteins that activate endothelial cell growth, two growth factors in particular, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), are expressed by many tumors and appear important in contributing to tumor growth and promoting tumor spread throughout the body. Several compounds that block VEGF or its receptor are now in **clinical trials**.

See also Angiogenesis inhibitors.

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Human papilloma virus

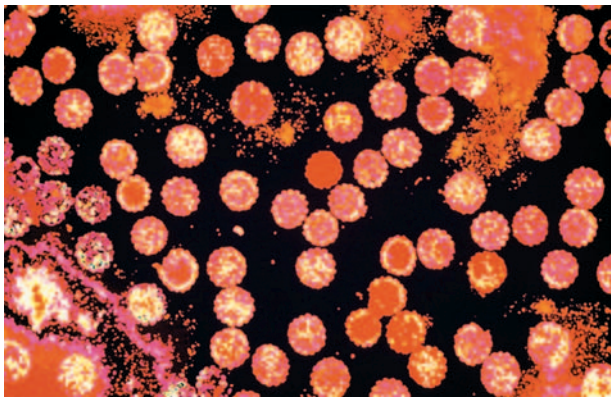
Definition

Human papilloma viruses (HPV) are a large group of related viruses, some of which play a part in the development of cervical epithelial cancers. HPV is also associated with skin cancer, cancers of the mouth, and anal cancers.

More recently, it has been suggested that HPV may be associated with an increased risk of lung cancer. In addition, a group of researchers at a cancer research center in Seattle reported in 2004 that smoking appears to increase the risk of anal cancer in women as well as men infected with HPV who practice anal sex.

Description

The family of human papilloma viruses includes a large number of genetically related viruses. Many of these cause warts, including the warts commonly found on the skin. Another group of HPV preferentially infect the mucosal surfaces of the genitals, including the penis, vagina, vulva, and cervix. These are spread among adults by sexual contact. One group of HPV that infect the genitals causes soft warts, often designated condylomata acuminata. These genital warts are quite common



Transmission electron micrograph of human papilloma virus, magnified 40,000 times. HPV is the cause of warts, including genital warts, and has been implicated in cervical cancer. *(Custom Medical Stock Photo. Reproduced by permission.)*

KEY TERMS

Ablative—Also known as "ablation" and referring to the surgical removal of lesions associated with HPV.

Biopsy—The removal of a small bit of tissue for diagnostic examination

Cervical intra-epithelial neoplasia (CIN)—A precancerous condition in which a group of cells grow abnormally on the cervix but do not extend into the deeper layers of this tissue.

Colposcopy—Procedure in which the cervix is examined using a special microscope.

Condylomata acuminata (singular, condyloma acuminatum)—The medical term for infectious warts on the genitals caused by HPV.

Cryotherapy—The use of extreme cold to destroy tissue.

Epithelial—Referring to the epithelium, the layer of cells forming the epidermis of the skin and the surface layer of mucous membranes.

High-risk HPV type—A member of the HPV family of viruses that is associated with the development of cervical cancer and precancerous growths.

Pap smear—A test that checks for abnormal cells that can lead to cervical cancer.

and rarely if ever become cancerous. The most common of these low-risk HPV types are designated HPV 6 and 11. The second group of viruses, termed high-risk HPV types, is associated with the development of **cervical cancer**. Individuals infected with these viruses are at higher risk for the development of precancerous lesions. Typically, infection with these viruses is common in adolescents and women in their twenties, and usually do not result in cancerous growth. The most common high-risk HPV is type 16. The appearance of abnormal cells containing high-risk HPV types is seen most frequently in women over the age of 30 who have abnormal Pap smears.

It is possible that other viruses work together with human papilloma viruses to produce precancerous changes in tissue. Cases of tongue cancer have been reported in which HPV was found together with Epstein-Barr virus, or EBV.

HPV infections are very common. At some point in their lives, greater than 75% of people are infected with HPV, making HPV the most common sexually transmitted disease. According to the Centers for Disease Control and Prevention (CDC), 20 million Americans are infected with HPV as of 2004, with 6.2 million new cases occurring each year.

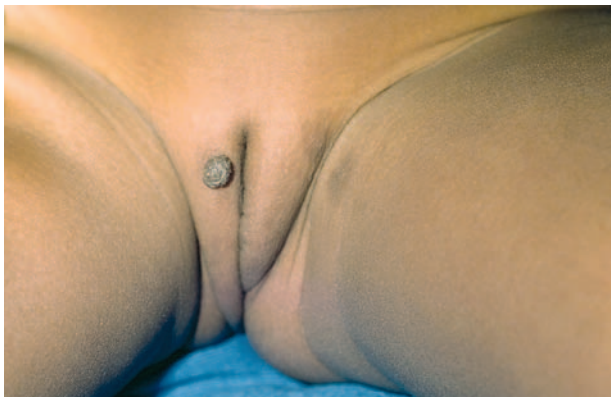
In general, HPV infections do not cause any obvious symptoms, which increases the likelihood of sexual transmission. Genital warts will occur in 1 or 2 of every 100 people. Abnormal Pap smears with atypical cells due to HPV can occur in 2–5% of women. If untreated, these women are at increased risk to develop cervical cancer. Virtually all cases of cervical cancer involve high-risk HPV types. It is believed that most cervical cancers take about five years to progress from early cellular changes to an invasive, life-threatening cervical cancer. It is not fully understood why most infections with high-risk HPV are of short duration, while a small percentage persist and eventually transform cervical cells to a state of cancerous growth.

In addition to producing precancerous lesions in some patients, HPV infections in women are a health concern because they can be transmitted to the respiratory tract of a baby during childbirth. This type of HPV infection may lead to juvenile-onset recurrent respiratory papillomatosis (JO-RRP), in which papillomas or warts form in the child's airway, producing hoarseness or partial blockage of the windpipe. As of 2004, surgery is the usual treatment for JO-RRP, but the warts often recur and require additional surgery to remove them. Cidofovir and interferon are often given as adjuvant treatments for this disease as of the early 2000s. JO-RRP is a serious illness, leading to death in a significant number of affected children.

The relationship among HPV, precancerous cellular changes, and cervical cancer have led to the suggestion that testing for the presence of HPV can be a useful

QUESTIONS TO ASK THE DOCTOR

- If my Pap smear is abnormal, do you think I should have an HPV test?
- Based upon my Pap smear result and HPV testing, when should I have my next Pap smear?
- What can I do to decrease my risk of becoming (re)infected with HPV?



Large brown genital wart of a female. *(Custom Medical Stock Photo. Reproduced by permission.)*

addition to Pap smears. Pap smears involve microscopic analysis of cells removed from the cervix. The results of these tests are generally reported as normal, or consistent with the presence of cancer or a precancerous condition. Patients receiving the latter diagnosis usually are treated, either by excisional or ablative therapy surgery or some other means, in order to remove the tumor or precancerous lesion. In some cases the cytologist or pathologist examining a Pap smear reports a "borderline" result when abnormal cells are observed, but it is not possible to distinguish whether the changes seen are due to early precancerous changes, or inflammation caused by some infectious agent or irritant. In these cases, some physicians and scientists believe that testing for the presence of HPV can help to identify those women who should be closely followed for the development of early cancerous lesions, or who should undergo colposcopy, a procedure to examine the cervix for precancerous lesions. These cancer precursors, termed cervical intraepithelial neoplasia (CIN) when identified early, before they have become invasive, can almost always be completely removed by minor surgery, essentially curing the patient before the cancer has had a chance to develop. The cervical tissue removed, which includes the precancerous tissue, is examined as part of a **biopsy** to confirm the diagnosis, and if requested by a doctor, can be tested for the presence of high-risk HPV types. This does not occur often.

Treatments

The only accepted treatment for HPV-related lesions is removal or eradication by surgery, lasers, cryotherapy, or electrocauterization. Since the incidence of latent and recurrent infections is high, the eradication of HPV is not always 100% effective. It is essential to be aware that HPV is a sexually transmitted disease and women must engage in safe sex practices to decrease the risk of spreading the virus or becoming re-infected. The development of an HPV vaccine that would render individuals resistant to infection by at least some of the high-risk HPV types is a matter of considerable interest. It is possible that such a vaccine will be available by 2010. As of 2004, a phase I study of a vaccine for HPV type 18, which causes 70% of cervical cancers, is under way at the University of Iowa.

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Warren Maltzman, Ph.D.
Rebecca J. Frey, Ph.D.

Hydrocodone *see* **Opioids**

Hydrocortisone *see* **Corticosteroids**

Hydromorphone *see* **Opioids**

Hydroxyurea

Definition

Hydroxyurea, also known by its trade name Hydrea, is an antineoplastic agent, meaning it is used to treat cancer. It is taken orally.

Purpose

Hydroxyurea is used to treat the following conditions:

- Melanoma
- **Chronic myelocytic leukemia** that is resistant to other therapies
- Ovarian cancer that is recurrent, metastatic or inoperable.
- Squamous cell carcinoma of the head and neck, excluding the lip. (In this case, hydroxyurea is given with radiation therapy.)
- Sickle cell anemia
- Other: Hydroxyurea has shown promise in the management of thrombocytosis, a condition in which platelet levels are abnormally high

Description

Hydroxyurea belongs to antimetabolites, a group of compounds that interfere with the production of nucleic acids. Hydroxyurea exerts its anticancer activity by inhibiting ribonucleotide reductase, an enzyme required for DNA synthesis. When used in conjunction with **radiation therapy**, the effectiveness of hydroxyurea increases because it also inhibits the ability of cells damaged by radiation to repair themselves.

Recommended dosage

Hydroxyurea dosages are calculated based on a person's weight as milligrams per kilogram (mg/kg). Doctors will usually use whichever value is lowest—the patient's actual weight or the patient's ideal weight—to calculate dosages. The drug is not given if white blood cell levels drop below 2500 mm^3, or if red blood cell levels drop below 100,000 mm^3. Usually, bone marrow recovery is rapid, and few doses are missed. Hydroxyurea is usually given for six weeks before its effectiveness can be adequately evaluated.

Hydroxyurea is administered in a capsule form, each containing 500 mg of the drug. If a patient is unable to swallow the capsule, its contents can be dissolved in a glass of water and swallowed immediately. The drug will not completely dissolve in water. Dosages have not been established for children in part because the cancers for which hydroxyurea is useful do not normally occur in that age group.

In the treatment of solid tumors, such as ovarian cancers, patients are usually given 80 mg/kg once every three days. Alternatively, a dose of 20–30 mg/kg may be given every day.

In **head and neck cancers** also treated with radiation, 80 mg/kg of hydroxyurea is given once every three days. The drug should be started a week before radiation therapy begins, and should continue for some time after radiation therapy.

When it is used to treat resistant chronic myelocytic leukemia, hydroxyurea is given in the dosage of 20–30 mg/kg once a day.

In thrombocytosis, doses of 15–30 mg/kg taken once a day are usually effective. Platelet levels return to a normal level within two to six weeks of therapy. In more severe cases, doses of 1.5–3.0 grams per day have been given with plateletpheresis, a procedure that removes platelets from the blood.

KEY TERMS

Mucositis—A painful inflammation of the mucous membranes.

Mutagen—An agent capable of causing DNA changes.

Myelosuppression—Diminished bone marrow activity resulting in decreased red blood cells, white blood cells, and platelets.

Plateletpheresis—A procedure in which platelets are removed from whole blood.

Precautions

This drug should not be administered to a person who has had a previous allergic reaction to it. Liver and kidney function should be evaluated prior to, and during, treatment. The drug may interfere with certain lab tests. For example, creatinine levels may be elevated. Patients taking hydroxyurea should stay well-hydrated, drinking up to 12 glasses per day of water or other fluids.

Hydroxyurea is potentially mutagenic, meaning that it causes mutations in DNA. Patients taking the drug should discuss the potential effects on their future conception plans. Hydroxyurea should not be administered to pregnant women, and women taking the drug should use birth control methods to prevent pregnancy. Hydroxyurea is excreted in breast milk; therefore, women taking the drug should not breast-feed.

Side effects

Hydroxyurea and radiation therapy each cause adverse side effects. When they are used together, the incidence and severity of side effects may increase.

Bone marrow suppression is the major side effect of hyroxyurea therapy, and may develop within two days of the first dose. Blood tests are performed routinely to monitor for changes. Usually, leukopenia (decreased white blood cells) develops first. Reduced red blood cells and platelets can also occur, but generally not as frequently. If anemia develops, it should be corrected with whole blood transfusions. Hydroxyurea causes red blood cell abnormalities that are not severe and that do not reduce the red blood cell survival time.

Gastrointestinal symptoms are not as common as **myelosuppression** and are usually mild. These symptoms may include nausea, vomiting, **diarrhea**, and constipation. Usually, medications can control **nausea and vomiting**. **Mucositis**, a painful swelling of the mucous membranes, may also develop, especially if the patient is undergoing radiation treatment to the head and neck. Mucositis can be managed with medicated mouthwashes, good oral hygiene, and hydration to keep the mouth moist.

Headache and dizziness may occur. With long-term use, skin changes, such as hyperpigmentation of the skin and nails, have also been reported.

Hydroxyurea has also been linked to leg ulcers. Studies suggest that leg ulcers have been reported mainly in older patients who might be at an increased risk. There have also been reports of hydroxyurea causing leg ulceration when it is used in psoriasis for a prolonged period.

Interactions

Patients at risk for bone marrow suppression should inform their doctor about all medications they are taking, both prescription and non-prescription. Many over-the-counter medications contain aspirin, which acts as a blood-thinner, increasing the potential for bleeding. Patients with reduced platelets should not take aspirin.

Tamara Brown, R.N.

Hypercalcemia

Description

Hypercalcemia is an abnormally high level of calcium in the blood, usually more than 10.5 milligrams per deciliter of blood. It is the most common life-threatening metabolic disorder associated with cancer.

Calcium plays an important role in the development and maintenance of bones in the body. It is also needed in tooth formation and is important in other body functions. As much as 99% of the body's calcium is stored in bone tissue. A healthy person experiences a constant turnover of calcium as bone tissue is built and reshaped. The remaining 1% of the body's calcium circulates in the blood and other body fluids. Calcium in the blood plays an important role in the control of many body functions, including blood clotting, transmission of nerve impulses, muscle contraction, and other metabolic activities.

Cancer-caused hypercalcemia produces a disruption in the body's ability to maintain a normal level of calcium. This abnormally high level of calcium in the blood

develops because of increased bone breakdown and release of calcium from the bone. The disorder occurs in approximately 10-20% of all cancer cases. The most common cancers associated with hypercalcemia are breast, prostate, and lung cancer, as well as **multiple myeloma** or other tumors with extensive **metastasis** to the bone. It may also occur in patients with head and neck cancer, cancer of unknown primary, **lymphoma**, leukemia, kidney cancer, and gastrointestinal cancer. Hypercalcemia most commonly develops as a late complication of cancer, and its appearance constitutes an emergency.

Several clinical symptoms are associated with cancer-related hypercalcemia. Symptoms may appear gradually and often look like signs of other cancers and diseases. The symptoms of hypercalcemia are not only related to the elevated level of calcium in the blood, but—more importantly—to how rapidly the hypercalcemia develops. The severity of the symptoms is often dependent upon factors such as previous cancer treatment, reactions to medications, or other illnesses a patient may have. Most patients do not experience all of the symptoms of hypercalcemia, and some may not have any signs at all. Rapid diagnosis of hypercalcemia may be complicated because the symptoms are often nonspecific and are easily ascribed to other factors. These symptoms include:

- decreased muscle tone and muscle weakness
- delirium, disorientation, incoherent speech, and psychotic symptoms such as hallucinations and delusion
- constipation
- **fatigue**
- poor appetite, nausea and/or vomiting
- frequency of urination and increased thirst
- pain

Causes

The fundamental cause of cancer-related hypercalcemia is increased movement of calcium out of the bones and into the bloodstream, and secondarily, an inadequate ability of the kidneys to get rid of higher calcium levels. Normally, healthy kidneys are able to filter out large amounts of calcium from the blood, getting rid of the excess that is unneeded by the body and keeping the amount of the calcium the body does need. However, the high levels of calcium in the body caused by cancer-related hypercalcemia may cause the kidneys to become overworked, thus making them unable to excrete the excess. Another problem is that some tumors produce a substance that may cause the kidneys to get rid of too little calcium.

Two types of cancer-caused hypercalcemia have been identified: osteolytic and humoral. Osteolytic occurs because of direct bone destruction by a primary or metastatic tumor. Humoral is caused by certain factors secreted by malignant cells, which ultimately cause calcium loss from the bones. Certain types of hormonal therapy may precipitate hypercalcemia and the use of some diuretics may contribute to the disorder.

Because immobility causes an increase in the loss of calcium from bone, cancer patients who are weak and spend most of their time in bed are more prone to hypercalcemia. Cancer patients are often dehydrated because they take in inadequate amounts of food and fluids and often suffer from **nausea and vomiting**. Dehydration reduces the ability of the kidneys to remove excess calcium from the body, and therefore is another contributing factor in the development of hypercalcemia in cancer patients.

Treatments

Individuals at risk for developing hypercalcemia may be the first to recognize symptoms, such as fatigue. The patient and family should be aware of the signs and symptoms so that a health care professional can be notified as early as possible should they occur. Patients can take several preventative measures like ensuring adequate fluid intake, controlling nausea and vomiting, maintaining the highest possible mobility, and avoiding drugs that affect the functioning of the kidneys. This includes avoiding those medications containing calcium, vitamin D, or vitamin A. Since absorption of calcium is usually decreased in individuals with hypercalcemia, dietary calcium restriction is unnecessary.

The mortality rate for untreated hypercalcemia is quite high. Early diagnosis and prompt treatment are essential. The magnitude of hypercalcemia and the severity of symptoms is usually the basis for determining what type of treatment is indicated.

For those patients who have mild hypercalcemia, are experiencing no symptoms, and have cancer that is responsive to treatment, giving intravenous fluids and observing the patient may be all that is necessary to treat the condition. If the patient is experiencing symptoms or has a cancer that is expected to respond poorly to treatment, then medication to treat the hypercalcemia should be initiated. Additional treatment focuses on controlling nausea and vomiting, encouraging activity, and avoiding any medication that causes drowsiness.

In treating moderate or severe hypercalcemia, replacing fluids is the first treatment intervention. Though providing fluid replacement will not restore normal calcium levels in all patients, it is still the most important initial step. Improvement in mental status and nausea and

KEY TERMS

Calcium—A silvery-yellow metal that is the most abundant mineral in the human body. Calcium and phosphorous combine as calcium phosphate, the hard material of bones and teeth.

Humoral hypercalcemia—An abnormally elevated blood calcium level caused by factors released from cancer cells, ultimately causing the loss of calcium from bone.

Osteolytic hypercalcemia—An abnormally elevated blood calcium level caused by destruction of bone by a primary or metastatic tumor.

vomiting is usually apparent within 24 hours for most patients. However, rehydration is only a temporary measure. If the cancer is not treated, then drugs that will help to control the hypercalcemia are necessary. Many drugs are used to treat hypercalcemia, including **calcitonin**, **plicamycin** (formerly mithramycin), **gallium nitrate**, and **bisphosphonates**. Bisphosphonates are some of the most effective drugs for controlling hypercalcemia. Loop diuretics like furosemide are often given because they help to increase the excretion of excess serum calcium. For severe hypercalcemia that is complicated by kidney failure, dialysis is an option. Because of the large amounts of intravenous fluids given to treat hypercalcemia, the health care team will carefully observe for any signs of overhydration or other electrolyte imbalances.

The severity of hypercalcemia determines the amount of treatment necessary. Severe hypercalcemia should be treated immediately and aggressively. Less severe hypercalcemia should be treated according to the symptoms. A positive response to the treatment is exhibited by the disappearance of the symptoms and a decreased level of calcium in the blood. Mild hypercalcemia does not usually need to be treated aggressively. After calcium levels return to normal, urine and blood should continue to be checked often to make certain the treatment is still working.

Alternative and complementary therapies

There are no known proven alternative treatments for cancer-related hypercalcemia. Some of the medications used are more effective than others, and the patient and family should discuss which ones are the most appropriate for the patient's needs.

Hypercalcemia usually develops as a late complication of cancer, and its appearance is very serious. The outlook is often quite grim. However, it is not clear if death occurs because of the hypercalcemia crisis or because of the advanced cancer. Because hypercalcemia is often a complication that occurs in the final stages of cancer, the decision to treat it depends upon the overall goals of treatment determined by the patient, family, and physician. The natural course of untreated hypercalcemia will progress to loss of consciousness and coma. Some patients may prefer this at the end of life rather than have unrelieved suffering and/or untreatable symptoms. It is therefore important for the patient and caregivers to discuss what supportive care measures are wanted.

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Deanna Swartout-Corbeil, R.N.

Hypercoagulable states, Trousseau's syndrome, Blood clots *see* **Hypercoagulation disorders**

Hypercoagulation disorders

Description

Hypercoagulation disorders (or hypercoagulable states or disorders) cause an increased tendency for clotting of the blood. In normal hemostasis (the stoppage of bleeding) clots form at the site of the blood vessel's injury. However, in hypercoagulation disorders the clots can develop in circulating blood. This may put a patient at risk for obstruction of veins and arteries (phlebitis, thrombosis, or thrombophlebitis). The hypercoagulable state and thrombophlebitis is common cases of cancer involving solid tumors such as pancreatic, breast, ovarian, and **prostate cancer**.

Hypercoagulation disorders can cause clots throughout the body's blood vessels, a condition known as thromboembolic disease. Thromboembolic disease can lead to infarction (death of tissue as a result of blocked blood supply to the tissue). Other serious results of hypercoagulation make this a dangerous condition. Clotting (thrombosis) in the veins and arteries leading to the lungs can prevent blood flow, causing sudden and severe

loss of breath and chest pain. These clots, called pulmonary embolisms, are potentially fatal. Clots in the blood vessels of the brain can result in a stroke, and clots in the heart's blood vessels can result in a heart attack.

Symptoms of hypercoagulation disorders include swelling or discoloration of the limbs, pain or tenderness of the skin, visible obstructions in the surface veins, and ulcers of the lower parts of the legs.

The diagnosis of hypercoagulation disorders is completed with a combination of physical examination, **imaging studies**, and blood tests. The presence of deep clots can be determined using Doppler ultrasound examination—special x-ray techniques called venography or arteriography (in which a solution is injected into the blood vessel to aid in imaging), or a specific type of blood pressure test called plethysmography. There are a number of blood tests that can determine the presence or absence of proteins, clotting factors, and platelet counts in the blood. Among the tests used to detect hypercoagulation is the Antithrombin III assay. Protein C and Protein S concentrations can be diagnosed with immunoassay or plasma antigen level tests.

KEY TERMS

Antithrombin—Any substance that counters the effect of thrombin. Thrombin is an enzyme that converts fibrinogen into fibrin, leading to blood coagulation.

Congenital—A condition or disorder present at birth.

Hemostasis— The arrest of bleeding.

Heparin—An anticoagulant, or blood clot dissolver.

Phlebitis—Inflammation of a vein.

Polycythemia—A condition characterized by an overabundance of red blood cells.

Thrombophlebitis—Inflammation of the vein with the formation of a thrombosis (blood clot).

Thrombosis—Formation of a clot in the blood that either blocks, or partially blocks, a blood vessel. The thrombus may lead to infarction (death of tissue due to a blocked blood supply).

Causes

Hypercoagulation disorders are associated with cancer of the pancreas. About half of patients with pancreatic cancer experience incidence of thrombosis. Approximately 10% of patients with pancreatic cancer develop a specific type of hypercoagulation disorder known as migratory thrombophlebitis, or Trousseau's syndrome. In Trousseau's syndrome the blood vessels become inflamed and clots in the blood vessels spontaneously appear and disappear. Other types of cancer may also result in hypercoagulation disorders.

In order for blood coagulation to occur, platelets (small, round fragments in the blood) help contract blood vessels to lessen blood loss and also to help plug damaged blood vessels. The conversion of platelets into actual clots is a complicated process involving proteins that are identified clotting factors. The factors are carried in the plasma, or liquid portion, of the blood. Proteins C and S are two of the clotting factors that are present in the plasma to help regulate or activate parts of the clotting process. It is believed that pancreatic tumors produce chemicals that promote clotting, or coagulation, of the blood (procoagulants), or that they activate platelet function. It is also possible that tumors interfere with the functions of proteins C and S.

Treatments

The treatment for patients with hypercoagulation disorders varies depending upon the severity of the clotting and the other conditions it may have caused. Medications may include blood thinners (anticoagulants) such as **heparin** and **warfarin**, which prevent the formation of new blood clots; antiplatelet drugs such as aspirin; or thrombolytic drugs to dissolve existing clots. Pain medications and nonsteroidal anti-inflammatory medications may be given to reduce pain and swelling. **Antibiotics** will be prescribed if infection has occurred.

Resources

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Paul A. Johnson, Ed.M.

Hyperthermia

Definition

Hyperthermia is the use of therapeutic heat to treat various cancers on and inside the body.

Purpose

The purpose of hyperthermia is to shrink and hopefully destroy cancer without harming noncancerous cells. It can be used to treat cancer in many areas of the body, including the brain, thyroid, lung, breast, and prostate. It is thought that high temperatures, up to 106 degrees Fahrenheit, can help shrink cancerous tumors. Hyperthermia is starting to be more widely used because it does not have side effects like other forms of cancer treatment such as radiation or **chemotherapy**. In some instances, hyperthermia is used at the same time with other forms of cancer therapy.

Through years of research, it has been found that the effectiveness of some forms of **radiation therapy** and chemotherapy are enhanced when combined with hyperthermia.

Although the treatment was considered experimental 15–20 years ago, its proponents believe that the treatment has been accepted by many physicians, and that use of hyperthermia will increase as more cancer centers install the high-tech equipment necessary for regional and whole body hyperthermia. (Currently, cancer care centers offering this treatment are limited.) The American Cancer Society acknowledged that hyperthermia can make the cancer cells of some cancers more responsive to treatment, but still considers the treatment experimental, especially in whole-body form. The National Institutes of Health are sponsoring ongoing **clinical trials** studying hyperthermia.

Precautions

Patients who have extensive **metastasis** (spreading of the cancer throughout their body) may not be good candidates for hyperthermia. Patients need to be free of major infections and able to tolerate the high temperatures of the treatment. Caution must be used when areas of the body are heated with external heat sources such as heating pads to avoid potentially dangerous burns.

Description

Hyperthermia can be used on the body from very small areas of the body to the entire body itself. Local hyperthermia refers to heating just one area of body, usually where the tumor is located. Heat can be applied from outside the body using microwaves or high-frequency radio waves. Heat can be applied from inside the body or even inside the tumor itself by the use of thin, heated wires, small tubes filled with hot water, or implanted microwave antennae.

If heat is used to treat an entire organ or limb, it is referred to as regional hyperthermia. High-energy magnets or other devices that produce high energy, and thus heat, are placed over the larger areas to be heated. Another method of regional hyperthermia is the use of perfusion. Hyperthermia perfusion uses the patient's own blood; the blood is removed, heated outside the body, then pumped back into the area that contains the cancer.

For treatment of cancers that have spread throughout the body, whole-body hyperthermia can be considered. Various methods are used to heat up a patient's entire body, including warm-water or electric blankets, hot wax, or thermal chambers which are very much like incubators used to warm newborn babies, except much larger.

Preparation

There are generally no advance preparations needed for a patient considering the use of hyperthermia.

Risks

The major risks of hyperthermia use are pain and external burns. Heat applied directly to the skin can cause minor discomfort to significant pain, especially when high temperatures are used. Blistering and actual burning of the skin can also occur at higher temperatures, although with careful application of the hyperthermia, these side effects are very rare.

Normal results

The goal of hyperthermia is to control the growth and shrink hyperthermia-sensitive tumors. As stated earlier, hyperthermia can also be used to help sensitize tumors to other cancer treatment modalities such as radiation and chemotherapy.

Abnormal results

There are generally no abnormal results seen with the use of hyperthermia. Side effects, such as pain and burning from external heat sources, can be minimized with careful application of the heat.

Resources

BOOKS

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I

Ibritumomab

Definition

Ibritumomab is a radioimmunotherapy used to treat **non-Hodgkin's lymphoma** (NHL).

Purpose

Ibritumomab is used to treat individuals with low grade follicular NHL that has failed to respond or that has stopped responding to the drug **rituximab** (Rituxan).

NHL is a cancer that arises in the organs of the lymph system. It is the most common type of **lymphoma** in the United States. The lymph system is important in creating and transporting blood cells called lymphocytes that fight infection throughout the body. The major organs of the lymph system are the spleen, thymus, tonsils, and bone marrow. These organs produce several different kinds of cells that fight infection. The major ones are called T-cells and B-cells. Ibritumomab specifically targets both mature and immature B-cells.

In NHL, abnormal (cancerous) lymphocytes grow out of control. So many of these abnormal lymphocytes develop that they prevent other immune system cells and blood vessel from forming. There are several types of NHL. One form is called follicular lymphoma. In this form, the cancerous cells clump together. They may grow quickly, in which case the disease is called a high-grade lymphoma, or they may grow slowly, in which case the cancer is called low-grade lymphoma.

Standard treatments for NHL include **chemotherapy**, **radiation therapy**, stem cell therapy, and a newer form of therapy called biologic therapy. Biologic therapy uses the biopharmaceutical rituximab. Ibritumomab is used in patients with low-grade B-cell NHL who have failed to respond or who have relapsed after standard treatment.

Description

Ibritumomab, which is also called ibritumomab tiuxetan, is manufactured in the United States and sold under the brand name Zevalin by IDEC Pharmaceuticals. It was approved for use in February 2002 and was the first radioimmunotherapy approved by the United States Food and Drug Administration (FDA). Generic substitutes are not available, and currently there is only one American manufacturer.

Radioimmunotherapy is a form of biologic therapy that combines a protein that attaches to the target cell with a small dose of radioactive material that disrupts and kills the cell. Unique proteins called antigens exist on the surface of every cell. The body monitors these proteins, and when it recognizes a cell as foreign or defective, it creates other antigen-specific proteins called antibodies to attach to the unwanted cells and disable them. With NHL, this system of protection fails and defective cancerous cells are allowed to continue growing.

Ibritumomab is an antibody made of mouse (murine) protein that comes from Chinese hamster ovary cells. It binds with the a protein called CD20 that is found on the surface of both normal and malignant B-cells. Ibritumomab alone does not kill B-cells, so it is bound to a radioactive material, either Indium-111 (In-111) or Yttrium-90 (Y-90). The role of ibritumomab is to deliver the radioactive material to specific target cells and bind it there. The radioactive rays given off by IN-111 or Y-90 disrupt the cell's functions, resulting in cell death. This therapy kills both healthy and cancerous B-cells.

Recommended dosage

Ibritumomab is given only in a two-step cycle in conjunction with another non-radioactive antibody called rituximab. Rituximab attacks the same B-cells as ibritumomab but does not deliver a dose of radioactive material to the cell. The two-step cycle of administration of ibritumomab is intended to occur only once.

The material needed for the therapeutic administration of ibritumomab is sold under the name Zevalin. The ibritumomab carrier antibody is mixed with the radioactive material by the physician shortly before use.

Step 1 includes a single dose of rituximab. The dose is determined by the patient's body size. Rituximab is infused slowly into a vein while the physician watches for hypersensitivity reactions. Within four hours following administration of rituximab, a single dose of 5.0 milliCuries (mCi) ibritumomab tiuxetan that contains the radioactive material In-111 is injected intravenously (IV) over a period of 10 minutes.

Step 2 follows seven to nine days after Step 1. The patient is given another IV dose of rituximab, again based on body size. Within four hours following the rituximab, the patient is injected with a dose of radioactive ibritumomab Y-90. This dose is also based on body size up to a total maximum allowable dose of 32.0 mCi. This completes the active part of the therapy, but patients must continue to have their blood count monitored for several months, as the therapy continues to kills cells for weeks.

Precautions

People who are allergic to any type of mouse (murine) protein, rituximab, yttrium chloride or indium chloride should not use this therapy. Ibritumomab can cause harm to the developing fetus and should not be used by pregnant women. Women should use birth control for 12 months after receiving this therapy. It has not been established whether this therapy is safe to use in breastfeeding women. A pediatric dose has not been established.

Zevalin is radioactive when it is being administered, and care should be taken to minimize exposure of patients and health care providers.

Side effects

Side effects are many and varied. Serious but rare side effects include:

- potentially fatal infusion hypersensitivity reactions, usually to the first dose of rituximab, that can cause low blood pressure, difficulty breathing, heart attack, and anaphylactic shock
- severe drop in platelet count (**thrombocytopenia**) or neutrophil count (**neutropenia**); uncontrolled bleeding
- development of secondary malignancies that arise from the therapy

More common but less serious side effects include:

- susceptibility to infections; **fever** or chills
- nausea, vomiting, **diarrhea**, black, tarry stools
- loss of appetite
- anemia
- joint pain
- dizziness
- increased cough or hoarseness
- rash, swelling, or puffiness around the face and neck

KEY TERMS

Anaphylactic shock—A whole body allergic reaction that is often fatal.

Malignant—Cancerous.

Neutrophil—A type of blood cell important to fighting infection.

Non-Hodgkin's lymphoma—A cancer of the lymph system that causes the accumulation of large numbers of defective (cancerous) immune system cells.

Platelet—A white blood cell that produces proteins that help blood clot.

Radioimmunotherapy—A treatment in which a radioactive material is delivered to specific cells by using a protein that binds to the surface of the target cells.

Interactions

It is important to tell the physician about all prescription medications, over-the counter medications, and herbal or alternative remedies that are being taken before treatment with Zevalin is begun. No formal drug interaction studies have been completed, however, Zevalin therapy does interfere with blood clotting and should not be used while individuals are taking blood thinners such as **warfarin** (Coumadin) or clopidogrel bisulfate (Plavix). Individuals who have a very low platelet count may not be able to use this therapy.

Individuals should not be vaccinated with a live virus vaccine prior to or soon after receiving this therapy. The interaction of live virus **vaccines** and this therapy has not been investigated, but it is recommended that individuals receiving ibritumomab avoid people who have recently been vaccinated with live virus oral polio vaccine.

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Idarubicin

Definition

Idarubicin is a medication that kills cancer cells.

Purpose

Idarubicin is approved to treat only one single cancer, acute myelocytic leukemia (AML) in adults. Recent research suggests that using idarubicin rather than the more traditional **daunorubicin** in treating AML results in higher rates of complete remission (CR) and longer survival for patients. CR is the total elimination of all diseased cells detectable following therapy. The Food and Drug Administration (FDA) has not approved idarubicin as treatment for **acute lymphocytic leukemia** (ALL).

Much research involving idarubicin is now being conducted. Some of this has involved acute lymphocytic leukemia (ALL) as well as AML. For example, a recent study was conducted in patients with either AML or ALL who had received **bone marrow transplantation** and then relapsed. Patients received a combination of **cytarabine**, idarubicin, and **etoposide**, as well as a medicine called G-CSF (filgrastim). This treatment achieved a high CR rate in these patients.

Another recent study looked at the use of idarubicin in children with AML. All of the children received cytarabine and etoposide. In addition, some of the children received idarubicin, while some received daunorubicin. Overall, patients in both groups fared equally well in terms of survival length. However, patients who had larger numbers of cells known as blasts (immature cells) tended to do better if they received idarubicin rather than daunorubicin. In addition, high-risk patients tended to do better with idarubicin than with daunorubicin. No subgroup of patients achieved better outcomes with daunorubicin than with idarubicin.

For older patients with acute nonlymphocytic leukemia, treatment with Idarubicin is effective and has acceptable side effects. According to recent research from Italy, "There is growing interest in autologous stem cell transplantation (ASCT) for elderly patients with acute myeloid leukemia (AML). While mortality and toxicity from ASCT have been reduced, relapse rate is still high.

Description

Idarubicin is an antibiotic, although doctors do not use this drug to attack infections. Its only use is to kill cancer cells. It does so by affecting how the DNA of cancer cells work.

KEY TERMS

Bilirubin—A pigment produced when the liver processes waste products. A high bilirubin level causes yellowing of the skin.

Blasts—Immature cells

Complete remission (CR)—Complete remission is the total elimination of all diseased cells detectable following therapy.

Necrosis—The sum of the morphological changes indicative of cell death. It may affect groups of cells or part of a structure or an organ.

Recommended dosage

In the treatment of AML, 12 mg of idarubicin per square meter may be given over a period of two to three days every three weeks in combination with other medications. Patients with liver problems may be given lower doses than other patients receive. Idarubicin is not typically given by mouth, as an insufficient amount of the medication would be transported through the stomach wall if this were done. Rather, this medication is usually administered through an intravenous (IV) procedure. During this time, it circulates widely throughout the body.

A new formulation of idarubicin has been developed. This permits idarubicin to be taken orally. However, this formulation is currently available only in France and only for older patients who are not good candidates for intensive intravenous treatment. There is little information currently available on the effectiveness of this oral formulation. The studies that have been performed suggest that it is less effective than other formulations of idarubicin.

Precautions

Idarubicin may be associated with excessive toxicity in patients with congestive heart failure, liver function characterized by a high bilirubin level, or prior chest radiation to the heart.

Side effects

Like daunorubicin and **doxorubicin**, idarubicin may adversely affect the patient's heart. However, doctors are not certain how much of the drug it takes to cause such harm and, therefore, how to limit dosage so that such harm is not caused. However, idarubicin appears to be less likely to cause heart damage than similar drugs such as daunorubicin and doxorubicin. Another

serious side effect that limits how much of the drug is given to patients is its potential adverse effect upon the bone marrow, where blood cells are produced.

Idarubicin may cause nausea and vomiting, baldness (alopecia), and stomach problems. In addition, idarubicin may cause blistering if extravasation occurs. Extravasation is when **chemotherapy** gets outside of the vein during infusion. If this occurs, the drug may cause severe local pain, swelling, or tissue necrosis that may require plastic surgery.

Patients receiving idarubicin in conjunction with certain other anticancer drugs may develop a type of leukemia. However, this is extremely rare.

In the few studies that have been conducted on the oral formulation of idarubicin, the most prominent side effects seen are low blood cell counts, nausea, vomiting, **diarrhea**, and **alopecia**.

Bob Kirsch

Ifosfamide

Definition

Ifosfamide is an anticancer (antineoplastic) agent. It also acts as a suppressor of the immune system. It is available under the brand name IFEX.

Purpose

Ifosfamide is approved by the Food and Drug Administration (FDA) to treat germ cell **testicular cancer**. It is generally prescribed in combination with another medicine (**mesna**), which is used to prevent the bladder problems that may be caused by ifosfamide alone.

Ifosfamide also has activity against other cancers and is prescribed in practice for these cancer types:

- pancreatic cancer
- stomach cancer
- soft-tissue sarcoma
- Ewing's sarcoma
- acute and chronic lymphocytic leukemia
- bladder cancer
- bone cancer
- breast cancer
- cervical cancer
- head and neck cancers
- lung cancer
- lymphomas
- neuroblastomas
- ovarian cancer
- **Wilms' tumor**

Description

Ifosfamide chemically interferes with the synthesis of the genetic material (DNA and RNA) of cancer cells by cross-linking of DNA strands, which prevents these cells from being able to reproduce and continue the growth of the cancer.

Recommended dosage

Ifosfamide may only be taken as an injection into the vein. The dosage prescribed varies widely depending on the patient, the cancer being treated, and whether or not other medications are also being taken. Examples of common doses for adults are: 50 mg per kg per day, or 700 to 2000 mg per square meter of body surface area for five days every three to four weeks. Another alternative regimen is 2400 mg per square meter of body surface area for three days or 5000 mg per square meter of body surface area as a single dose every three to four weeks. Examples of common dosing regimens for children are: 1200 to 1800 mg per square meter of body surface area per day for three to five days every 21 to 28 days; 5000 mg per square meter of body surface area once every 21 to 28 days; or 3000 mg per square meter of body surface area for two days every 21 to 28 days.

Precautions

Ifosfamide can cause an allergic reaction in some people. Patients with a prior allergic reaction to ifosfamide should not take this drug.

Ifosfamide should always be taken with plenty of fluids.

Ifosfamide can cause serious birth defects if either the man or the woman is taking this drug at the time of conception or if the woman is taking this drug during pregnancy. Contraceptive measures should be taken by both men and women while on this drug. Because ifosfamide is easily passed from mother to child through breast milk, breast feeding is not recommended during treatment.

Ifosfamide suppresses the immune system, and its excretion from the body is dependent on a normal

functioning kidney and liver. For these reasons, it is important that the prescribing physician is aware of any of the following pre-existing medical conditions:

- a current case of, or recent exposure to, chicken pox
- herpes zoster (shingles)
- all current infections
- kidney disease
- liver disease

Also, because ifosfamide is such a potent immunosuppressant, patients taking this drug must exercise extreme caution to avoid contracting any new infections.

Side effects

Inflammation and irritation of the bladder, causing blood in the urine, is the most common and severe side effect of ifosfamide. However, this side effect can be prevented and controlled with the administration of the bladder protectant drug mesna and vigorous hydration with intravenous fluids before, during, and after **chemotherapy**. Patients should also urinate frequently (at least every 2 hours) to enhance removal of the drug from the body, and drink 2 to 3 liters of fluids a day for 2 to 3 days after discontinuation of the chemotherapy.

Other common side effects of ifosfamide are:

- confusion
- hallucinations
- drowsiness
- dizziness
- temporary hair loss (alopecia)
- increased susceptibility to infection
- increased risk of bleeding (due to a decrease of the platelets involved in the clotting process)
- nausea and vomiting (can be prevented with prescribed antiemetics)

Less common side effects include:

- increased coloration (pigmentation) of the skin and fingernails
- loss of appetite (anorexia)
- diarrhea
- nasal stuffiness
- skin rash, **itching**, or hives

A doctor should be consulted immediately if the patient experiences any of these side effects:

- painful or difficult urination

KEY TERMS

Antineoplastic—A drug that prevents the growth of a neoplasm by interfering with the maturation or proliferation of the cells of the neoplasm.

Neoplasm—New abnormal growth of tissue.

- increase in frequency or feeling of urgency to urinate
- blood in the urine
- blood in the stool
- severe diarrhea
- mental status changes such as confusion, drowsiness, or hallucinations
- signs of infection such as cough, sore throat, **fever** and chills
- shortness of breath
- chest or abdominal pain
- pain in the lower back or sides
- unusual bleeding or bruising
- tiny red dots on the skin

Interactions

Ifosfamide should not be taken in combination with any prescription drug, over-the-counter drug, or herbal remedy without prior consultation with a physician.

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Imaging studies

Definition

Imaging studies are tests performed with a variety of techniques that produce pictures of the inside of a patient's body. They have become indispensable tools in cancer screening and detection.

Description

Imaging tests are performed using sound waves, radioactive particles, magnetic fields, or x rays that are detected and converted into images after passing through body tissues. Dyes are sometimes used as contrasting agents with x-ray tests so that organs or tissues not seen with conventional x rays can be enhanced. The operating

principle of the various techniques is based on the fact that rays and particles interact differently with various types of tissues, especially when cancerous growths are present. In this way, the interior of the body can be visualized and pictures are provided of normal structure and function as well as of abnormalities.

Imaging tests differ from endoscopic tests, which are carried out with a flexible, lighted piece of tubing connected to a viewing lens or camera.

Imaging studies are used to detect cancer in its early stages in a procedure called screening. Screening is performed in patients who have no obvious cancer symptoms. Imaging studies are also used to locate tumors in patients who have symptoms which the physician may wish to investigate further so as to distinguish between benign growths or cancerous tumors. They are also used to determine the extent of a cancer and indicate how a given treatment is unfolding. As such, they represent crucial tools for cancer diagnosis and management.

Major imaging techniques

Computed tomography scan (CT scan)

Computed tomography scans show a cross-section of a part of the body. In this technique, a thin beam is used to produce a series of exposures detected at different angles. The exposures are fed into a computer which overlaps them so as to yield a single image analogous to a slice of the organ or body part being scanned. A dye is often injected into the patient so as to improve contrast and obtain images that are clearer than images obtained with x rays.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging also produces cross-sectional images of the body using powerful magnetic fields instead of radiation. MRI is especially useful to detect and locate cancers of the liver and the central nervous system, which occur in the brain or the spinal cord. It uses a cylinder housing a magnet which will induce the required magnetic field. The patient lies on a platform inside the scanner. The magnetic field aligns the hydrogen atoms present in the tissue being scanned in a given direction. Following a burst of radio-frequency radiation, the atoms flip back to their original orientation while emitting signals which a fed into a computer for conversion into a two- or three-dimensional image. Dyes can also be injected into patients to produce clearer images.

Mammography

Mammography is an x-ray examination of the breast. It is often used as a screening tool to detect breast abnormalities and cancers before they can be felt. Mammograms (the image produced) are acquired using an x-ray machine working at lower radiation levels than conventional **x ray**. The breast is compressed between two plates so as to allow the low-level x-ray radiation to produce a film.

Nuclear scan

Nuclear scans, also called radionuclide imaging or scintigraphy, use substances called tracers or radionuclides that release low levels of radioactivity. The test is based on the principle that the tracers will be absorbed to a different degree by different tissues, thus allowing to distinguish between normal and cancerous tissues. Common **nuclear medicine scans** for cancer patients to receive are bone scans; liver, spleen, and thyroid scans are also frequently performed.

Position emission tomography (PET)

Positron emission tomography uses a form of sugar that contains a radioactive atom which emits particles called positrons. The positrons are absorbed to a different extent by cells varying in their metabolic rate. PET scans are especially useful for brain imaging studies and are widely applied to the assessment of the spread of cancers in the lungs. PET scans are also being used experimentally in the assessment of breast, colon, rectum, and ovarian cancers.

X rays

X rays produce shallow images of certain specific organs or tissues. X rays are a form of high-energy radiation and tissues of the body can absorb it to varying degrees. For example, bones absorb less x rays than soft tissue. After passing through the body, the x rays are directed on a film, where the dense tissue appears as a white shadow, thus providing contrast with the soft tissue, which produces a darker impression on the film. X rays produce a single image.

Chest x rays are used to detect lung and bronchial cancers, and also to evaluate a patient's symptoms, such as shortness of breath. Other types of x rays, such as abdominal x rays, may also be ordered to assess a patient's symptoms, but are not used as cancer screening tools as chest x rays may be used.

X rays with dye studies

Dye studies are usually performed by injecting the contrasting agent in the patient's circulatory system or in the target organ. These studies are used to produce angiograms, cystograms, myelograms, lymphangiograms and fistulograms.

ANGIOGRAM An angiogram is an examination of the blood vessels using x rays. It is usually performed with intravenous injection of fluorescein dye followed by multiframe photography. The doctor inserts a small tube (catheter) into the blood vessel and then injects the dye that makes the vessels visible when the x-ray pictures are acquired.

CYSTOGRAM A cystogram is a scan of the bladder and ureters. The ureters are passages that lead from the kidneys to the bladder. A catheter is inserted into the bladder or a radioactive material, called a radioisotope, is introduced into the bladder. An oral cholecystogram (OCG) is an x-ray examination of the gallbladder, the organ that helps release bile into the small intestine for the digestion of fats. The gallbladder is not seen well on conventional x-ray pictures and special tablets are ingested by mouth to enhance contrast.

MYELOGRAM A myelogram is an x ray of the spine and spinal cord. The spinal cord is the nerve tissue enclosed in the vertebral column that goes from the bottom of the brain to halfway down the back. During a myelogram, x-ray dye is injected into the spinal fluid and mixes with it, flowing around the spinal cord which can then be seen and recorded on x-ray film.

LYMPHANGIOGRAM A lymphangiogram is an x ray of the lymphatic system, also carried out with dye injection for contrasting purposes. It is used to screen for lymph node involvement in cancer.

FISTULOGRAM A fistula is an abnormal passage within body tissue. For example, a fistula may connect two organs inside the body that are not normally connected. A fistula may also lead from an internal organ inside the body to the surface outside. Examples are: between the skin and the bowel (enterocutaneous fistula), between the stomach and the colon (gastrocolic fistula). A fistulogram is an x-ray examination of this abnormal passage. The contrasting agent is injected directly into the fistula so that it will show up on x-ray pictures.

Fluoroscopy

Fluoroscopy is one of the oldest areas of diagnostic radiology. It is similar to x ray in that a small dose of x rays is directed through a body part but the image obtained is displayed on a monitor rather than on the conventional x-ray film. The fluoroscope provides images of internal body parts as they move, similar to a movie. A continuous x-ray beam is passed through the body part being examined, and is transmitted to an image-intensifying tube, which is a TV-like monitor so that the body part and its motion can be seen in detail.

KEY TERMS

Cancer screening—A procedure designed to detect cancer even though a person has no symptoms, usually performed using an imaging technique.

CT scan—An imaging technique that uses a computer to combine multiple x-ray images into a two-dimensional cross-sectional image

Mammography—An imaging technique producing x-ray pictures of the breast called mammograms.

MRI—A special imaging technique used to image internal parts of the body, especially soft tissues.

PET—A highly specialized imaging technique using radioactive substances to identify active tumors.

Radionuclide imaging—An imaging technique in which a radionuclide is injected through tissue and a display is obtained from a scanner device.

During fluoroscopy, the patient is placed between the x-ray source and the monitor. The live images generated by the x-ray source strike the image-intensifying tube and allow doctors to see the size, shape, and structure of a patient's internal structures. Because the radiation is blocked more effectively by dense tissue, such as that of a tumor, the result is a dark shadow of the tumor on the screen, against a light background. Most fluoroscopy devices include television or video cameras attached to the image-intensifier tube. The camera output can be digitized and sent through a computer for image enhancement.

In fluoroscopic studies, the radiologist can either insert an intravenous (IV) catheter (hollow tube inserted into blood vessels or into an organ) to **biopsy** a tumor or he can use a contrast agent to visualize the organ or area of interest. The contrast agent allows the image to be viewed more clearly. Contrast agents may be introduced into the patient's body by injection, swallowing, or an enema. Fluoroscopic exams include the following types of tests: barium swallow, **barium enema**, and intravenous pyelography (also called intravenous urography).

BARIUM SWALLOW Used for GI series. The patient drinks a chalky, milkshake-like concoction containing barium, which coats the esophagus and stomach. The barium absorbs the x rays so that the lining of the upper digestive tract can be clearly seen. In barium x rays, fluoroscopy allows the physician to see the movement of the intestines as the barium moves through them.

BARIUM ENEMA In a lower GI series, the patient receives a barium enema, which coats the intestines and rectum. A gap in the image in the stomach or small intestine could indicate an ulcer and bubbles in the normally smooth large intestinal lining may be abnormal growths.

INTRAVENOUS PYELOGRAPHY (IVP) Pyelography, also called urography, consists of several x rays of all the urinary system, meaning kidneys, ureter, bladder and urethra. A contrast agent is injected through a vein, to make the organs visible for the x rays.

See also Screening test; Ultrasonography.

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Imatinib mesylate

Definition

Imatinib mesylate is an enzyme inhibitor used for cancer therapy. Imatinib mesylate is also known as STI571 and is sold under the brand name, Gleevec. It was given the name STI571 during early development. STI stands for signal transduction inhibitor.

Purpose

Imatinib mesylate is approved by the U. S. Food and Drug Administration to treat a rare cancer called chronic myeloid leukemia (CML). (CML is also called chronic myelogenous leukemia or **chronic myelocytic leukemia**, as well.)

Description

Imatinib mesylate is the first drug of its kind developed. It fights cancer by turning off an enzyme called tyrosine kinase that causes CML cells to lose their ability to die so they can multiply at an abnormal rate. Its function is different from other cancer drugs because it specifically targets an enzyme that allows the growth of CML cells. This drug has been shown to significantly reduce the number of cancer cells in the blood and bone marrow of treated patients.

Patients who are diagnosed with CML in the three phases of disease can be treated with imatinib mesylate. Chronic myeloid leukemia appears to respond within one to three months following administration of this drug.

Recommended dosage

A doctor experienced in the treatment of patients with CML should initiate therapy.

To minimize the risk of gastrointestinal irritation, imatinib mesylate should be taken with food and a large glass of water. The recommended dosage varies according to clinical circumstances and phase of disease, but generally ranges between 300 and 600 mg per day. As long as the patient continues to benefit, treatment should be continued.

Precautions

Studies have not been performed with imatinib mesylate to determine if it is a carcinogen (cancer causing); therefore it is not known whether this drug may cause mutations or may have cancer-causing effects. In

addition, imatinib mesylate's safety and effectiveness has not been established in pediatric patients.

- Fluid retention and edema. If patients experience swelling or weight gain from water retention, they should inform their doctor and should be closely monitored. Signs and symptoms of fluid retention should be closely monitored and patients should be weighed regularly. Appropriate treatment must be provided if an unexpected rapid weight gain occurs. The likelihood of edema is increased with higher doses and in those over age 65 years.
- gastrointestinal irritation
- hematologic toxicity (toxicity of the blood)
- hepatotoxicity (toxicity of the liver)
- toxicities from long-term use

Side effects

Commonly reported side effects include **nausea and vomiting**, muscle cramps, edema (water retention), skin rash, **diarrhea**, heartburn, and headache. Serious side effects occur less frequently, but if they occur may include severe edema liver toxicity, and the potential for bleeding especially in the elderly.

Interactions

Imatinib mesylate interacts with many other drugs. In some cases, side effects may be increased because imatinib mesylate might increase blood levels of certain drugs. Alternatively, imatinib mesylate may decrease blood levels of the drugs, thus reducing their effectiveness. In addition, the blood levels of imatinib mesylate may rise or fall because of other drugs. Therefore, side effects of imatinib mesylate may be increased or effectiveness may be reduced. The patient must discuss all of their medications with their doctor due to many potential drug-drug interactions.

CYP3A4 is an enzyme that is predominately responsible for the metabolism of imatinib mesylate. The following drugs or families of drugs may interact with imatinib mesylate:

- Inhibitors of the CYP3A4 family, such as ketoconazole, itraconazole, erythromycin.
- Co-medications that induce CYP3A4, such as **dexamethasone**, **phenytoin**, **carbamazepine**, rifampicin, phenobarbital or St. John's Wort). No formal studies have been conducted on these medications and imatinib mesylate together.
- CYP3A4 substrates, such as **cyclosporine** or pimozide.
- CYP3A4 metabolized drugs, such as certain HMG-CoA reductase inhibitors, triazolo-benzodiazepines, and dihydropyridine calcium channel blockers.
- Warfarin. Patients needing anticoagulant therapy while taking imatinib mesylate should be prescribed low-molecular weight or standard heparin. This list is not all-inclusive of all possible interactions. Patients must inform their doctors of any drugs they are taking in order to avoid drug interactions.

Investigators also evaluated the effect of St. John's wort, an herb used to treat mild to moderate depression, on the pharmacokinetics of imatinib. Studies showed that the administration of St. John's wort along with imatinib mesylate reduced absorption and increased elimination of imatinib, reducing drug exposure by as much as 42%. Since clinical efficacy of imatinib is dependent on drug dose and concentration, the interaction with St. John's wort could result in a loss of therapeutic effect. Therefore, the concurrent use of St. John's wort and imatinib should be avoided.

See also Low molecular weight heparins.

Crystal Heather Kaczkowski, MSc.

KEY TERMS

CYP3A4—An enzyme that is predominately responsible for the metabolism of imatinib mesylate.

Enzyme—Any protein that acts as a catalyst, increasing the rate of a chemical reaction.

Kinase—An enzyme.

Leukemia—A type of cancer in which the bone marrow produces an excessive number of abnormal (leukemic) white blood cells. White blood cells protect the body against infection but the abnormal cells suppress the production of normal white blood cells.

Tumor—An abnormal mass of tissue that serves no purpose. Tumors may be either benign (non-cancerous) or malignant (cancerous).

Tyrosine—A non-essential amino acid. Amino acids are the building blocks of protein. They are the raw materials used by the body to make protein. Tyrosine is labeled "nonessential" because, when the amino acids are lacking in the diet, they can be manufactured in the body.

Immune globulin

Definition

Immune globulin is a concentrated solution of antibodies, pooled from donated blood, which is sometimes given to cancer patients whose own immune systems are either not working or are suppressed as a side effect of treatment. Immune globulin can also be called gamma globulin; in the United States some of the brand names are Gamimune, Gammagard, Gammar-P, Iveegam, Polygam, Sandoglobulin, and Venoglobulin.

Purpose

A healthy human body produces proteins called antibodies that act to destroy microorganisms (bacteria and viruses) that invade the body. Some cancer patients, due to the illness itself or side effects of treatment, become depleted of these proteins and therefore susceptible to serious infections. Immune globulin is given to these patients to restore their body's immunity. The use of immune globulin in this way is also called passive immunization. For example, immune globulin is given to bone marrow transplant recipients to prevent the development of severe bacterial infections while their own immune systems are not functioning, and **chronic lymphocytic leukemia** patients (of the type whose antibody-producing cells are the malignant cells) are given immune globulin to prevent the recurrent infections these patients sometimes suffer. Use in this disorder also allows the use of aggressive **chemotherapy** that will destroy the patient's own cancerous antibody-producing cells.

Immune globulin is also used to treat other diseases such as **Eaton-Lambert Syndrome**, a rare neurological disorder that sometimes occurs in association with small cell lung cancer called Eaton-Lambert syndrome, an autoimmune disease in which a patient's own antibodies attack nerve cells. The use of immune globulin appears to cause the body to reduce its own production of antibody, thereby improving the neurological disorder.

Description

Immune globulin primarily consists of antibody proteins of the type called IgG or gamma, although the solution may contain small amounts of other antibody types as well as sugars, proteins, and salt.

It is produced by pooling donated blood from at least 1000 people who have been tested to be free of blood-borne diseases like HIV or hepatitis. The antibody proteins are then separated out of the whole blood, and the pH of the immune globulin solution is adjusted to match the normal pH of blood. The preparation is also treated to remove any contaminants, including infectious bacteria or viruses.

Recommended dosage

The dose of immune globulin used varies with the specific problem that it is being used for. When immune gobulin is used in patients with Eaton-Lambert Syndrome, the effective dose is usually about 1 g/kg of body weight/day. (One gram equals 0.035274 ounce; one kilogram equals 2.2046 pounds.) When used to counteract immunodeficiency, the dose is designed to produce an antibody level that stays at an effective threshold over a period of time.

When immune globulin is given to bone marrow transplant recipients, it is usually begun at the time of the transplant and continued for 100 days thereafter, with the objective of maintaining the level of IgG in the patient's blood above 400 mg per deciliter. (A deciliter equals 3.38 fluid ounces.) In patients with chronic lymphocytic leukemia (B-cell type) the target threshold for antibodies in the patient's blood is usually about 600 mg/dL. Although the amount required to maintain these levels varies from patient to patient (because different patients metabolize the drug at different rates) a dose between 10 and 200 mg/kg of body weight, given every 3-4 weeks, is usually sufficient.

Immune globulin is usually given intravenously, although intramuscular shots are available.

Precautions

Some people may have experienced severe reactions, including allergy-type reactions, to other antibody preparations. Generally, these people should not be given intravenous immune globulin. Patients with deficiency of antibody IgA, specifically, should also avoid the use of immune globulin. People with a tendency to form blood clots, or those with kidney problems should also avoid the use of this product, especially if elderly. While many pregnant women have been treated with immune globulin for different problems that have occurred during their pregnancy, since the method of action and specific effects on the fetus are not completely understood, pregnant women should avoid the use of immune globlulin unless it is clearly necessary. Any patient who is given immune globulin should be watched carefully, and epinephrine should be kept available in case a severe allergic reaction is experienced. Immune globulin which was made to be given through intramuscular injection should never be administered intravenously.

KEY TERMS

Autoimmune disease—A disease in which the body produces an immunologic reaction against itself.

Epinephrine—A medication used to treat heart failure and severe allergic reactions.

Immunoglobulins—An antibody of a specific type. Five main types are produced, known as IgA, IgD, IgE, Ig G, and IgM. Most antibody in the blood is IgG.

Intramuscular administration—A shot usually in the hip or arm, in which medication is delivered into a muscle.

Intravenous administration—Introduction of medication straight into a vein (commonly called IV).

Neurologic—Involving the nervous system.

Side effects

Administration of intramuscular immune globulin may result in tenderness, swelling, and possibly hives at the site of the injection.

Intravenous immune globulin may cause more severe reactions related to rapid introduction into the blood system. Possible side effects include headache, backache, aching muscles, **fever**, low blood pressure, and chest pain. More commonly, fever accompanied by chills or **nausea and vomiting** may be experienced. If these side effects occur, they are usually related to the immune globulin being administered too rapidly. If the rate of infusion is reduced, or if the infusion is stopped temporarily, negative effects will generally disappear. Rare, but potentially serious, side effects observed have been kidney failure and aseptic meningitis.

Interactions

Use of immune globulin may reduce the effectiveness of vaccinations (for example, measles, mumps, and rubella) for a few months following the use of the immune globulin preparation. Patients who have been given immune globulin should notify their doctors before any vaccinations are given. In addition, in some situations patients may need to have antibody levels measured to determine whether or not they have had previous infection with a specific microorganism. Use of immune globulin can create the false impression of prior exposure to the organism due to the donated antibodies in their blood.

See also Immunologic therapies

Wendy Wippel, M.S.

Immune response

Definition

The ability of any given cell in the body to distinguish self from nonself is called the immune response.

All cells in the body are recognized as self. Any microorganism (for example, a foreign body or tumor) that invades or attacks the cells is recognized as nonself—or foreign—requiring the immune system to mount a combat against the nonself.

Immune system

The immune system is comprised of a network of immune cells that are generated in the bone marrow stem cell (a cell whose daughter cells may develop into other types of cells). From stem cells different types of immune cells originate that can handle specific immune functions. Phagocytes (cell eaters), serve as the first line of defense, engulfing dead cells, debris, virus, and bacteria. Macrophages are an important type of phagocyte, often presenting the antigen—which is usually a foreign protein—to other immune cells and thus are also called "antigen-presenting cells" (APC). T and B lymphocytes, important immune-system cells, are also capable of recognizing the antigen and become activated. T lymphocytes are classified into two subtypes: killer T cells (also called cytotoxic T cells) and helper T cells. Killer T cells recognize and kill the infected or cancer cells that contain the antigen or the foreign protein. Helper T cells release cytokines (chemical messengers) upon activation that either directly destroy the tumor or stimulate other cells to kill the target (tumor). B lymphocytes produce antibodies after recognizing the antigens. The antibodies, which help protect the body from the antigen, are normally specific to that particular antigen. In cases of tumor the specific antibodies attach to tumor cells and, through various mechanisms, impair the functions of the tumor, ultimately leading to the death of the cancer cell.

In addition to these lymphocytes are natural killer (NK) cells that particularly perform the task of eliminating foreign cells. Natural killer cells differ from

killer T cells in that they target tumor cells and do not have to recognize an antigen before activation. These cells have been shown to be of potential use in treating cancer.

Immune system and cancer

The immune system serves as one of the primary defenses against cancer. When normal tissue becomes a tumor or cancerous tissue, new antigens develop on their surface. These antigens send a signal to immune cells such as the cytotoxic T lymphocytes, NK cells, and macrophages, which in turn directly kill the tumor cells or release substances like cytokines that may bring about tumor cell death. Thus, under normal circumstances, the immune system provides continued surveillance and eliminates cells that become cancers. However, tumors may survive by hiding or disguising their tumor antigens, or by producing substances that allow suppressor T cells (cells that block cytotoxic, or killer T cells that would normally attack the tumor) to proliferate (multiply).

Biological response modifiers in cancer therapy

Researchers have been working on stimulating the immune cells during cancer with substances broadly classified as biological response modifiers. Cytokines are one such substance. These are proteins that are predominantly released by immune cells upon activation or stimulation. During the 1990s the number of cytokines identified increased enormously and the functions associated with them are of immense potential in diagnostics and immune therapy. Some of the key cytokines that have proven therapeutic value in cancer are interleukin-2 (IL-2), Interferon gamma, and interleukin-12 (IL-12). Cytokines are normally injected directly to cancer patients; however, there are other cases where a cancer patient's own lymphocytes are modified under laboratory conditions and injected back into the patient. Examples of these are lymphokine-activated killer (LAK) cells and tumor-infiltrating lymphocytes (TILs). These modified cells are capable of devouring cancer cells.

Immunoprevention of cancer

Immunotherapy is emerging as one of the management strategies for cancer. However, established tumors or large masses of tumor do not respond well to immunotherapy. There is clinical evidence, however, that suggests that patients with minimal residual cancer cells (a few cells left after other forms of cancer treatment) are potential candidates for effective immunotherapy. In these cases immunotherapy often results in a prolonged tumor-free survival. Thus, immune responses can be manipulated to prevent recurrence, even though it does not destroy large tumors. Based on results of immunotherapy trials, most immune therapies are geared towards designing immunoprotective strategies such as cancer **vaccines**.

KEY TERMS

Antigen—Molecules or fragments of molecules that belong to a foreign invader that can elicit an immune response. These may include germs, toxins, and tissues from another person used in organ transplantation.

Cytokines—Proteins (chemical messengers) that are predominantly released by immune cells upon activation or stimulation that help bring about tumor cell death.

Stem cell—A cell whose daughter cells may differentiate (develop into other cell types).

Cancer vaccines

Cancer vaccines can be made either with whole, inactivated tumor cells, or with fragments or cell surface substances (called cell-surface antigens) present in the tumors. In addition to the whole cell or antigen vaccines, biological modifiers, like cytokines, serve as substances that boost immune response in cancer patients.

Since cancer vaccines are still under clinical evaluation, caution should be exercised while choosing them as the mode of therapy. The cancer care team will provide further insight on whether or not cancer vaccine or cytokine therapy will be beneficial after they assess the patient's stage and the various modes of treatments available.

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Immunoelectrophoresis

Definition

Immunoelectrophoresis, also called gamma globulin electrophoresis, or immunoglobulin electrophoresis, is a method of determining the blood levels of three major immunoglobulins: immunoglobulin M (IgM), immunoglobulin G (IgG), and immunoglobulin A (IgA).

Purpose

Immunoelectrophoresis is a powerful analytical technique with high resolving power as it combines separation of antigens by electrophoresis with immunodiffusion against an antiserum. The increased resolution is of benefit in the immunological examination of serum proteins. Immunoelectrophoresis aids in the diagnosis and evaluation of the therapeutic response in many disease states affecting the immune system. It is usually requested when a different type of electrophoresis, called a serum **protein electrophoresis**, has indicated a rise at the immunoglobulin level. Immunoelectrophoresis is also used frequently to diagnose **multiple myeloma**, a disease affecting the bone marrow.

Precautions

Drugs that may cause increased immunoglobulin levels include therapeutic gamma globulin, hydralazine, isoniazid, **phenytoin** (Dilantin), procainamide, oral contraceptives, methadone, steroids, and tetanus toxoid and antitoxin. The laboratory should be notified if the patient has received any vaccinations or immunizations in the six months before the test. This is mainly because prior immunizations lead to the increased immunoglobulin levels resulting in false positive results.

It should be noted that, because immunoelectrophoresis is not quantitative, it is being replaced by a procedure called immunofixation, which is more sensitive and easier to interpret.

Description

Serum proteins separate in agar gels under the influence of an electric field into albumin, alpha 1, alpha 2, and beta and gamma globulins. Immunoelectrophoresis is performed by placing serum on a slide containing a gel designed specifically for the test. An electric current is then passed through the gel, and immunoglobulins, which contain an electric charge, migrate through the gel according to the difference in their individual electric charges. Antiserum is placed alongside the slide to identify the specific type of immunoglobulin present. The results are used to identify different disease entities, and to aid in monitoring the course of the disease and the therapeutic response of the patient with such conditions as immune deficiencies, autoimmune disease, chronic infections, chronic viral infections, intrauterine fetal infections, multiple myeloma, and monoclonal gammopathy of undetermined significance.

There are five classes of antibodies: IgM, IgG, IgA, IgE, and IgD.

IgM is produced upon initial exposure to an antigen. For example, when a person receives the first tetanus vaccination, antitetanus antibodies of the IgM class are produced 10 to 14 days later. IgM is abundant in the blood but is not normally present in organs or tissues. IgM is primarily responsible for ABO blood grouping and rheumatoid factor, yet is involved in the immunologic reaction to other infections, such as hepatitis. Since IgM does not cross the placenta, an elevation of this immunoglobulin in the newborn indicates intrauterine infection such as rubella, cytomegalovirus (CMV) or a sexually transmitted disease (STD).

IgG is the most prevalent type of antibody, comprising approximately 75% of the serum immunoglobulins. IgG is produced upon subsequent exposure to an antigen. As an example, after receiving a second tetanus shot, or booster, a person produces IgG antibodies in five to seven days. IgG is present in both the blood and tissues, and is the only antibody to cross the placenta from the mother to the fetus. Maternal IgG protects the newborn for the first months of life, until the infant's immune system produces its own antibodies.

IgA constitutes approximately 15% of the immunoglobulins within the body. Although it is found to some degree in the blood, it is present primarily in the secretions of the respiratory and gastrointestinal tract, in saliva, colostrum (the yellowish fluid produced by the breasts during late pregnancy and the first few days after childbirth), and in tears. IgA plays an important role in defending the body against invasion of germs through the mucous membrane-lined organs.

IgE is the antibody that causes acute allergic reactions; it is measured to detect allergic conditions. IgD, which constitutes the smallest portion of the immunoglobulins, is rarely evaluated or detected, and its function is not well understood.

Preparation

This test requires a blood sample.

Aftercare

Because this test is ordered when either very low or very high levels of immunoglobulins are suspected, the

patient should be alert for any signs of infection after the test, including **fever**, chills, rash, or skin ulcers. Any **bone pain** or tenderness should also be immediately reported to the physician.

Risks

Risks for this test are minimal, but may include slight bleeding from the blood-drawing site, fainting or feeling lightheaded after venipuncture, or bruising.

Normal results

Reference ranges vary from laboratory to laboratory and depend upon the method used. For adults, normal values are usually found within the following ranges (1 mg = approximately .000035 oz. and 1 dL = approximately 0.33 fluid oz.):

- IgM: 60–290 mg/dL
- IgG: 700–1,800 mg/dL
- IgA: 70–440 mg/dL

Abnormal results

Increased IgM levels can indicate **Waldenström's macroglobulinemia**, a malignancy caused by secretion of IgM at high levels by malignant lymphoplasma cells. Increased IgM levels can also indicate chronic infections, such as hepatitis or mononucleosis and autoimmune diseases, like rheumatoid arthritis.

Decreased IgM levels can be indicative of AIDS, immunosuppression caused by certain drugs like steroids or dextran, or leukemia.

Increased levels of IgG can indicate chronic liver disease, autoimmune diseases, hyperimmunization reactions, or certain chronic infections, such as tuberculosis or sarcoidosis.

Decreased levels of IgG can indicate Wiskott-Aldrich syndrome, a genetic deficiency caused by inadequate synthesis of IgG and other immunoglobulins. Decreased IgG can also be seen with AIDS and leukemia.

Increased levels of IgA can indicate chronic liver disease, chronic infections, or inflammatory bowel disease.

Decreased levels of IgA can be found in ataxia, a condition affecting balance and gait, limb or eye movements, speech, and telangiectasia, an increase in the size and number of the small blood vessels in an area of skin, causing redness. Decreased IgA levels are also seen in conditions of low blood protein (hypoproteinemia), and drug immunosuppression.

KEY TERMS

Antibody—A protein manufactured by the white blood cells to neutralize an antigen in the body. In some cases, excessive formation of antibodies leads to illness, allergy, or autoimmune disorders.

Antigen—A substance that can cause an immune response, resulting in production of an antibody, as part of the body's defense against infection and disease. Many antigens are foreign proteins not found naturally in the body, and include germs, toxins, and tissues from another person used in organ transplantation.

Autoimmune disorder—A condition in which antibodies are formed against the body's own tissues, for example, in some forms of arthritis.

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Janis O. Flores

Immunohistochemistry

Definition

Immunohistochemistry is a method of analyzing and identifying cell types based on the binding of antibodies to specific components of the cell. It is sometimes referred to as immunocytochemistry.

Purpose

Immunohistochemistry (IHC) is used to diagnose the type of cancer and to help determine the patient's prognosis. In cases such as metastases or **carcinoma of unknown primary** origin, where it may be difficult to determine the type of cell from which the tumor originated, immunohistochemistry can identify cells by the characteristic markers on the cell surface. IHC can also help distinguish between benign and malignant tumors.

KEY TERMS

Antibody—A protein formed by the immune system to react with a specific antigen.

Antigen—Any protein that elicits a unique immune response.

Biopsy—A sample of tissue taken from a tumor to compare with other normal tissue.

Histology—The study of tissues.

QUESTIONS TO ASK THE DOCTOR

- What do you expect to learn from this test?
- What are the alternatives to this test?
- Are there any risks or complications?
- Are any special preparations required?
- Is hospitalization required?
- Is it possible that the test may give a false positive, a false negative, or unclear results?

Description

Immunohistochemistry requires a sample of tissue from a **biopsy**; usually the tissue sample is examined fresh, but frozen or chemically preserved material can be used. A blood sample or bone marrow may also be examined. The tissue sample is sliced extremely thinly, so that it is approximately one cell thick, then the sample is fixed onto a glass slide. The tumor cells in the sample have characteristic markers, or antigens, on their cell surfaces which can be used to help identify the specific type of tumor cell. Antibodies against these characteristic antigens are added to the sample on the slide, and the antibodies bind wherever the antigens are present. Excess antibody is then washed away. The antibodies that remain bound to the cell have labels on them that either fluoresce (glow) or undergo a chemical reaction that makes them visible by microscope. The pathologist is able to see the specially labeled tumor antigens as they appear in the patient's tissue.

The pathologist will try to assess the level of maturity of the tumor cells, which will help him to determine their origin. He will be checking for cell types that are found in an inappropriate part of the body, for example prostate cells in a lymph node. He will also look for cell characteristics that will indicate if the tumor is benign or malignant. Proteins involved in the replication of genetic material and cell growth may be present in greater amounts; for example, antibodies against the antigen Ki-67 are used to evaluate malignant melanomas, breast carcinomas, and **non-Hodgkin's lymphomas**. Hormone receptors may also be examined. The presence of receptors to estrogen and progesterone indicate a good prognosis for **breast cancer** patients. Pathologists may also look for an increase in tumor suppressor proteins. A wide variety of antibodies are available to help determine the origin of the tumor, whether it is growing rapidly, and whether it is a type of tumor that responds well to particular treatments.

Preparation

The physician will choose the type of sample to be taken based on the type of tumor. If the patient has a solid tumor, a tissue sample may be biopsied; if the entire tumor is being removed a biopsy may be taken during surgery. In this case the patient should prepare for the surgery or the biopsy as the physician suggests. A routine blood sample may also be required; in most cases, no additional preparation is required.

Aftercare

The only aftercare that might be required is from the sample collection process.

Risks

The risks associated with IHC are the risks associated with the sample collection, either the biopsy of the tumor or the drawing of blood. The only other concern is the possibility that the test could yield unclear results.

Normal results

Normal results will simply look like normal cells. The cells will have a high level of maturity and be located only in sites appropriate to their cell type. For example, analysis of lymph nodes will show only the cells that belong there, not cells that would normally be present in the breast. No specific tumor antigens will be present in increased numbers.

Abnormal results

An abnormal result would consist of cells which appear immature or poorly differentiated, or that are found in an inappropriate tissue for their cell type. The pathologist may test for the presence of a particular antigen, such as Ki-67, carcinoembryonic antigen (CEA), or prostate specific antigen (PSA). In this case, there may be a numerical standard value to compare normal to abnormal results and help the physician in determining prognosis.

See also Receptor analysis; Tumor markers.

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Racquel Baert, M.S.

Immunologic therapies

Definition

Immunologic therapy is the treatment of disease using medicines that boost the body's natural **immune response**. Some forms of immunologic therapy are intended to bypass the body's weakened immune system while others are intended to repair or direct it.

Purpose

Immunologic therapy is used to improve the immune system's natural ability to fight diseases such as cancer, hepatitis and AIDS. These drugs may also be used to help the body recover from immunosuppression resulting from treatments such as **chemotherapy** or **radiation therapy**.

Description

Most drugs in this category are synthetic versions of substances produced naturally in the body. In their natural forms, these substances help defend the body against disease. For example, **aldesleukin** (Proleukin) is an artificially made form of interleukin-2, which helps white blood cells work. Aldesleukin is administered to patients with kidney cancers and skin cancers that have spread to other parts of the body. **Filgrastim** (Neupogen) and **sargramostim** (Leukine) are versions of natural substances called colony stimulating factors, which drive the bone marrow to make new white blood cells. Another type of drug, epoetin (Epogen, Procrit), is a synthetic version of human **erythropoietin** that stimulates the bone marrow to make new red blood cells. **Thrombopoietin** stimulates the production of platelets, disk-shaped bodies in the blood that are important in clotting. **Interferons** are substances the body produces naturally using immune cells to fight infections and tumors. The synthetic interferons carry brand names such as Alferon, Roferon, or Intron A. Some of the interferons that are currently in use as drugs are Recombinant Interferon Alfa-2a, Recombinant Interferon Alfa-2b, Interferon Alfa-n1, and Interferon Alfa-n3. Alfa interferons are used to treat **hairy cell leukemia**, malignant **melanoma**, and AIDs-related **Kaposi's sarcoma**. In addition, interferons are also used for other conditions such as laryngeal papillomatosis, genital warts, and certain types of hepatitis.

Recommended dosage

The recommended dosage depends on the type of immunologic therapy. For some medicines, the physician will decide the dosage for each patient, taking into account a patient's weight and whether he/she is taking other medicines. Some drugs used in immunologic therapy are given only in a hospital, under a physician's supervision. For those that patients may give themselves, check with the physician who prescribed the medicine or the pharmacist who filled the prescription for the correct dosage.

Most of these drugs come in injectable form. These drugs are generally administered by the cancer care provider.

Precautions

Aldesleukin

This medicine may temporarily increase the chance of getting infections. It may also lower the number of platelets in the blood, and thus possibly interfering with the blood's ability to clot. Taking these precautions may reduce the chance of such problems:

- Avoid people with infections, if possible.
- Be alert to signs of infection, such as **fever**, chills, sore throat, pain in the lower back or side, cough, hoarseness, or painful or difficulty with urination. If any of these symptoms occur, get in touch with a physician immediately.
- Be alert to signs of bleeding problems, such as black, tarry stools, inky red spots on the skin, blood in the urine or stools, or any other unusual bleeding or bruising.
- Take care to avoid cuts or other injuries. Be especially careful when using knives, razors, nail clippers, and

other sharp objects. Check with a dentist for the best ways to clean the teeth and mouth without injuring the gums. Do not have dental work done without checking with a physician.

- Wash hands frequently, and avoid touching the eyes or inside of the nose unless the hands have just been washed.

Aldesleukin may make some medical conditions worse, such as chickenpox, shingles (**herpes zoster**), liver disease, lung disease, heart disease, underactive thyroid, psoriasis, immune system problems, and mental problems. The medicine may increase the chance of seizures (convulsions) in people who are prone to having them. Also, the drug's effects may be greater in people with kidney disease, because their kidneys are slow to clear the medicine from their bodies.

Colony stimulating factors

Certain drugs used in treating cancer reduce the body's ability to fight infections. Although colony stimulating factors help restore the body's natural defenses, the process takes time. Getting prompt treatment for infections is important, even while taking this medicine. Call the physician at the first sign of illness or infection, such as a sore throat, fever, or chills.

People with certain medical conditions could have problems if they take colony stimulating factors. People who have kidney disease, liver disease, or conditions caused by inflammation or immune system problems can worsen these problems with colony stimulating factors. Those who have heart disease may be more likely to experience side effects such as water retention and heart rhythm problems while taking these drugs. Finally, patients who have lung disease might increase their chances of suffering from shortness of breath. Those who have any of these medical conditions should check with their personal physicians before using colony stimulating factors.

Epoetin

Epoetin is a medicine that may cause seizures (convulsions), especially in people who are prone to having them. No one who takes these drugs should drive, use machines, or do anything considered dangerous in case of a seizure.

Epoetin helps the body make new red blood cells, but it is not effective unless there is adequate iron in the body. The physician may recommend taking iron supplements or certain **vitamins** that help supply the body with iron. It is necessary to follow the physician's advice in this instance—recommendations for iron in this case, as with any supplements should only come from a physician.

In studies of laboratory animals, epoetin taken during pregnancy caused birth defects, including damage to the bones and spine. However, the drug has not been reported to cause problems in human babies whose mothers take it. Women who are pregnant or who may become pregnant should check with their physicians for the most up-to-date information on the safety of taking this medicine during pregnancy.

People with certain medical conditions may have problems if they take this medicine. For example, the chance of side effects may be greater in people with high blood pressure, heart or blood vessel disease, or a history of blood clots. Epoetin may not work properly in people who have bone problems or sickle cell anemia.

Interferons

Interferons can add to the effects of alcohol and other drugs that slow down the central nervous system, such as antihistamines, cold medicine, allergy medicine, sleep aids, medicine for seizures, tranquilizers, some pain relievers, and muscle relaxants. They may also add to the effects of anesthetics, including those used for dental procedures. Those taking interferons should check with their physicians before taking any of the above.

Some people experience dizziness, unusual fatigue, or become less alert than usual while being treated with these drugs. Because of these possible problems, anyone who takes these drugs should not drive, use machines, or do anything else considered dangerous until they have determined how the drugs affect them.

Interferons often cause flu-like symptoms, including fever and chills. The physician who prescribes this medicine may recommend taking acetaminophen (Tylenol) before—and sometimes after—each dose to keep the fever from getting too high. If the physician recommends this, follow instructions carefully.

Like aldesleukin, interferons may temporarily increase the chance of getting infections and lower the number of platelets in the blood, leading to clotting problems. To help prevent these problems, follow the precautions for reducing the risk of infection and bleeding listed for aldesleukin.

People who have certain medical conditions may have problems if they take interferons. For example, the drugs may worsen some medical conditions, including heart disease, kidney disease, liver disease, lung disease, diabetes, bleeding problems, and mental problems. In people who have overactive immune systems, these drugs can even increase the activity of the immune

system. People who have shingles or chickenpox, or who have recently been exposed to chickenpox may increase their risk of developing severe problems in other parts of the body if they take interferons. People with a history of seizures or mental problems could at risk if taking interferon.

In teenage women, interferons may cause changes in the menstrual cycle. Young women should discuss this possibility with their physicians. Older people may be more sensitive to the effects of interferons. This may increase the chance of side effects.

These drugs are not known to cause fetal death, birth defects, or other problems in humans when taken during pregnancy. Women who are pregnant or who may become pregnant should ask their physicians for the latest information on the safety of taking these drugs during pregnancy.

Women who are breastfeeding their babies may need to stop while taking this medicine. Whether interferons pass into breast milk is not known. Because of the chance of serious side effects to the baby, breast-feeding while taking interferon is discouraged. Check with a physician for advice.

General precautions for all types of immunologic therapy

Regular physician visits are necessary during immunologic therapy treatment. This gives the physician a chance to make sure the medicine is working and to check for unwanted side effects.

Anyone who has had unusual reactions to drugs used in immunologic therapy should let the physician know before resuming the drugs. Any allergies to foods, dyes, preservatives, or other substances should also be reported.

Side effects

Aldesleukin

In addition to its helpful effects, this medicine may cause serious side effects. Generally, it is given only in a hospital, where medical professionals can watch for early signs of problems. Medical tests might be performed to check for unwanted effects.

Anyone who has breathing problems, fever, or chills while being given aldesleukin should check with a physician immediately.

Other side effects should be brought to a physician's attention as soon as possible:

- dizziness
- drowsiness
- confusion
- agitation
- depression
- **nausea and vomiting**
- **diarrhea**
- sores in the mouth and on the lips
- tingling of hands or feet
- decrease in urination
- unexplained weight gain of five or more pounds

Some side effects are usually temporary and do not need medical attention unless they are bothersome. These include dry skin; itchy or burning skin rash or redness followed by peeling; loss of appetite; and a general feeling of illness or discomfort.

Colony stimulating factors

As this medicine starts to work, the patient might experience mild pain in the lower back or hips. This is nothing to cause undue concern, and will usually go away within a few days. If the pain is intense or causes discomfort, the physician may prescribe a painkiller.

Other possible side effects include headache, joint or muscle pain and skin rash or **itching**. These side effects tend to disappear as the body adjusts to the medicine, and do not need medical treatment. If they continue, or they interfere with normal activities, check with a physician.

Epoetin

This medicine may cause flu-like symptoms, such as muscle aches, **bone pain**, fever, chills, shivering, and sweating, within a few hours after it is taken. These symptoms usually go away within 12 hours. If they do not, or if they are troubling, check with a physician. Other possible side effects that do not need medical attention are diarrhea, nausea or vomiting and fatigue or weakness.

Certain side effects should be brought to a physician's attention as soon as possible. These include headache, vision problems, increased blood pressure, fast heartbeat, weight gain and swelling of the face, fingers, lower legs, ankles or feet.

Anyone who has chest pain or seizures after taking epoetin should seek professional emergency medical attention immediately.

Interferons

This medicine may cause temporary hair loss (alopecia). While upsetting, it is not a sign that something is

seriously wrong. The hair should grow back normally after treatment ends.

As the body adjusts to the medicine many other side effects usually go away during treatment. These include flu-like symptoms, taste alteration, loss of appetite (anorexia), nausea and vomiting, skin rash, and unusual fatigue. If these problems persist, or if they interfere with normal life, check with a physician.

A few more serious side effects should be brought to a physician's attention as soon as possible:

- confusion
- difficulty thinking or concentrating
- nervousness
- depression
- sleep problems
- numbness or tingling in the fingers, toes and face

General caution regarding side effects for all types of immunologic therapy

Other side effects are possible with any type of immunologic therapy. Anyone who has unusual symptoms during or after treatment with these drugs should should contact the physician immediately.

Interactions

Anyone who has immunologic therapy should let the physician know all other medicines being taken. Some combinations of drugs may interact, that can increase or decrease the effects of one or both drugs or can increase the likelihood of side effects. Consultation with a physician is highly recommended to get the insight on whether the possible interactions can interfere with drug therapy or cause harmful effects.

Immunoprevention

Considering that most of the biological modifiers such as cytokines elicit immune response that inhibit incipient tumors before they are clinically evident, immunoprevention has been proposed as a recent strategy for combating cancer. Treatment involving immune molecules (such as cytokines) prepared synthetically or that are not produced by the patients themselves is called as passive immunotherapy. Conversely, a vaccine is a form of active immune therapy because it elicits an immune response in patients. A cancer vaccine may be made of whole tumor cell or of substances or fragments contained in the tumor called antigens.

Newer types of immunologic therapy that are still considered investigational as of 2003 include cell-based

KEY TERMS

AIDS—Acquired immunodeficiency syndrome. A disease caused by infection with the human immunodeficiency virus (HIV). In people with this disease, the immune system breaks down, increasing vulnerability to other infections and some types of cancer.

Bone marrow—Soft tissue that fills the hollow centers of bones. Blood cells and platelets (disk-shaped bodies in the blood that are important in clotting) are produced in the bone marrow.

Chemotherapy—Treatment of an illness with chemical agents. The term is usually used to describe the treatment of cancer with drugs.

Clot—A hard mass that forms when blood gels.

Dendritic cells—Immune system cells derived from a type of white blood cell called monocytes. Dendritic cells help to activate the B cells, helper T cells, and killer T cells in the immune system.

Hepatitis—Inflammation of the liver caused by a virus, chemical, or drug.

Immune response—The body's natural, protective reaction to disease and infection.

Immune system—The system that protects the body against disease and infection through immune responses.

Inflammation—Pain, redness, swelling, and heat that usually develop in response to injury or illness.

Psoriasis—A skin disease that manifests itself with itchy, scaly, red patches on the skin.

Seizure—A sudden attack, spasm, or convulsion.

Shingles—A disease caused by an infection with the Herpes zoster virus—the same virus that causes chickenpox. Symptoms of shingles include pain and blisters along one nerve, usually on the face, chest, stomach, or back.

Sickle cell anemia—An inherited disorder in which red blood cells contain an abnormal form of hemoglobin, a protein that carries oxygen. The abnormal form of hemoglobin causes the red cells to become sickle-shaped. The misshapen cells may clog blood vessels, preventing oxygen from reaching tissues and leading to pain, blood clots and other problems. Sickle cell anemia is most common in people of African descent and in people from Italy, Greece, India, and the Middle East.

therapies. Instead of using synthetic chemicals that resemble substances produced by the body, cell-based therapies use modified stem cells or dendritic cells as vaccines against cancer. Stem cells are undifferentiated cells whose daughter cells can develop into various types of specialized cells, while dendritic cells are cells that are able to initiate and modify the immune system's responses to cancer by activating B cells and T cells. Dendritic cells appear to offer a promising new form of immunotherapy for cancer.

Another investigational form of treatment is the development of cell-free tumor-specific peptide vaccines. Peptides are subunits of protein molecules that contain two or more amino acids. Peptide vaccines are intended to induce responses in the patient's T cells that inhibit tumor growth. As of late 2003, however, peptide-based tumor vaccines have been shown to shrink cancerous tumors only in patients with limited disease.

Adoptive immunotherapy

Adoptive immunotherapy involves stimulating T lymphocytes by exposing them to tumor antigens. These modified cells are grown in the laboratory and then injected into patients. Since the cells taken from a different individual for this purpose often results in rejection, patients serve both as donor and recipient of their own T cells. Adoptive immunotherapy is particularly effective in patients who have received massive doses of radiation and chemotherapy. In such patients, therapy results in immunosuppression (weakened immune systems), making them vulnerable to viral infections. For example, CMV-specific T cells can reduce the risk of cytomegalovirus (CMV) infection in transplant patients.

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Immunotherapy *see* **Immunologic therapies**

Implantable subcutaneous ports *see* **Vascular access**

Incontinence

Description

Incontinence is the loss of normal control of the bowel or bladder. Incontinence can involve the involuntary voiding of urine (urinary incontinence) or of stool and gas (fecal or bowel incontinence). There are several types of urinary incontinence. Those most frequently seen as side effects of cancer include overflow incontinence, urge incontinence, and stress incontinence. In rare cases incontinence occurs as the result of cancer, but more commonly it is a side effect of treatment. Because the subjects of bowel and bladder control are perceived as socially unacceptable, those affected with incontinence often feel ashamed or embarrassed by the problem. Instead of seeking medical attention, these individuals try to hide the problem or manage it themselves. For this reason, incontinence is sometimes referred to as "the silent affliction." Impacts of incontinence include low self-esteem, social withdrawal and isolation, and **depression**. In most cases incontinence can be successfully treated, so affected individuals should discuss the problem with a doctor.

Causes

Incontinence can result from damage to the muscle, nerves, or the structure of the body parts involved in the

control of voiding. Complex systems of hollow organs (such as the bladder) and tube-shaped structures (such as the rectum and urethra) work together to store and release waste. Special muscles, including sphincters, are especially important in maintaining the tight seals that hold in waste. When physical damage to muscle or organ structure occurs, the system can no longer maintain these tight seals, and waste can leak out.

Nerves carry messages between the brain and the bowel and bladder systems. Injury to these nerves, or the related part of the brain, interferes with the delivery of these messages, which can prevent the body from recognizing the signals telling it when to void. Without these signals and messages, an individual cannot coordinate the brain with the bowel and bladder systems, and incontinence results.

Several types of cancer and its treatments are associated with incontinence. Usually, it is the treatment of cancer that causes incontinence, rather than the cancer itself.

Prostate cancer

The treatment of **prostate cancer** is one of the most common causes of cancer-related urinary incontinence, largely because the prostate is located so closely to the nerves, muscles, and structures involved in urine control. Surgical removal of the prostate, or **prostatectomy**, carries the highest risk of urinary incontinence as a side effect; the risk from **radiation therapy** is somewhat lower. The incontinence (typically stress or urge incontinence) is often temporary, but in a small percentage of men it may be long lasting.

Prostate cancer itself seldom causes incontinence. However, this depends on the location and size of the cancer; a large cancerous prostate can interfere with the flow of urine and result in overflow incontinence.

Bladder cancer

Incontinence is only occasionally the direct result of **bladder cancer**, but it is a common side effect of some treatments. For early-stage cancer where treatment does not require the bladder to be removed, incontinence almost never occurs. But removal of the bladder and surrounding structures is often necessary to treat more advanced cancer. This requires creation of an artificial system for storing and releasing urine and carries a risk of long-term incontinence.

Colon cancer and rectal cancer

Muscles in the anal and rectal region largely control bowel evacuation, with the colon storing stool and gas.

KEY TERMS

Evacuation—Release of stool or gas from the bowel system.

Overflow incontinence—Slow leaking or dripping of urine from an overfilled bladder that may be unable to empty completely.

Sphincter—A circular muscle that relaxes and tightens to control the storage and release of bodily waste.

Stress incontinence—Involuntary loss of waste resulting from sudden pressure or force, such as by coughing, sneezing, laughing, or lifting an object.

Urethra—A tube-like structure allowing the passage of urine between the bladder and the outside of the body.

Urge incontinence—Involuntary loss of waste after feeling a strong, sudden need to void, without enough time to get to a toilet.

Voiding—Release of urine from the bladder system.

When these regions are removed or damaged during cancer treatment, or if injury to the related nerves occurs, fecal incontinence can result. Fecal incontinence is most commonly a side effect of surgery. Weakening of bowel muscles or damaging of nerves by radiation therapy can also cause incontinence, but this type is more likely to be mild and temporary, and will often improve as these areas heal. However, in some patients, radiation causes permanent and severe fecal incontinence.

Other causes

Loss of voluntary bowel and bladder control is less commonly associated with other cancers of the genital and urinary systems, mainly as a side effect of treatment. Incontinence can also result from cancer or treatment damage in the brain and spinal cord. Other cancers indirectly cause incontinence; for example, constant coughing from lung cancer can lead to stress incontinence. Very rarely, incontinence can be a side effect of certain medications.

Treatments and complementary therapies

The method of treatment depends on the cause and type of incontinence. Surgical treatment is usually reserved for severe or long-lasting incontinence. An artificial pouch for storing urine or stool can be placed inside the body as a substitute for a removed bladder, colon, or rectum. Placement of an artificial sphincter

successfully treats other cases. For mild or temporary incontinence, treatment may include medications, dietary changes, muscle-strengthening exercises, or behavioral training, such as establishing a time pattern for voiding. A small group of patients, however, requires a permanent colostomy or **urostomy**.

Electrical stimulation therapy, which targets involved muscles with low-current electricity, can be used to treat either urinary or fecal incontinence. Biofeedback uses electronic or mechanical devices to improve bladder or bowel control by teaching an individual how to recognize and respond to certain body signals.

Embarrassment may lead some people to manage the symptoms of incontinence themselves by wearing absorbent pads to prevent the soiling of their clothes. However, many treatments exist to successfully restore or improve control of bowel and bladder function, so individuals experiencing incontinence should speak to a doctor or nurse.

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Infection and sepsis

Description

Infection is characterized by an inflammatory response to the presence of microorganisms in the body. This response may include **fever**, chills, redness, swelling, pus formation, and other responses. The most common cause of illness and death in patients with cancer is infection. Patients with cancer who are treated with **chemotherapy**, **radiation therapy**, and/or surgery are at increased risk of developing an infection. Mortality, or death, from infection in cancer patients decreased during the late 1900s due to the development of new types of **antibiotics**, the use of hematopoietic growth factors (HGFs) which activate proliferation (multiplication) and maturation of blood cell lines, and due to the prophylactic (preventive) use of antifungal and antiviral agents. Blood cell lines, markedly decreased due to chemotherapy, are required to fight infections. Most infections in cancer patients are due to bacteria; however, fungal infections are usually the cause of fatal infections.

If left untreated, or if inadequately treated, infection can progress to sepsis. Sepsis is defined as a systemic (total body) inflammatory response to the presence of microorganisms in the body. Several conditions indicate sepsis, including a temperature of greater than 38 degrees Centigrade (100.4 Fahrenheit) or less than 36 degrees Centigrade (96.8 Fahrenheit), heart rate greater than 90 beats per minutes, and respiratory rate greater than 20 breaths per minute. The incidence rate of sepsis in cancer patients is estimated at 45%. Mortality rates from sepsis in cancer patients exceed 30%.

Causes

There are many possible causes of infection in the patient with cancer. For example, certain cancers interfere with the body's immune system response, which results in increased risk of infection to the patient. These cancer types include **acute leukemia**, **chronic lymphocytic leukemia**, **multiple myeloma**, **Hodgkin's disease**, and non-Hodgkin's lymphoma. Certain therapies used to treat cancer, such as chemotherapy (which interrupts bone marrow production of white blood cells, red blood cells, and platelets), radiation therapy, **bone marrow transplantation**, and treatments using **corticosteroids**, can lead to infection in the patient with cancer. The protein-calorie malnutrition that some cancer patients experience can result in suppression of the immune system, which results in increased risk for infection. Many cancer patients develop infections from procedures which break the integrity of the skin, which then leads to the introduction of microorganisms into the body. These procedures include common interventions in the care of cancer patients such as venipunctures, biopsies, insertion of urinary catheters, and use of long-term central venous catheters. Infection rates associated with long-term central venous catheter use in cancer patients is estimated to be as high as 60%. If the cancer patient's immune system is severely compromised, infection can occur from food sources, plants, and/or air the patient comes in contact with.

Myelosuppression is the term used to describe the decrease in numbers of circulating white blood cells (WBC), red blood cells (RBC), and platelets. Myelosuppression is often a side effect of treatment with chemotherapy and/or radiation therapy. Blood counts usually begin to fall one to three weeks after treatment with chemotherapy, depending upon the type of chemotherapy and the lifespan of the blood cell. The counts generally begin to recover to normal levels within two to three weeks. The neutrophil, which is a component of the white blood cells, is the body's first line of defense against infection caused by bacteria. When neutrophils are decreased a state of **neutropenia** exits. Neutropenia is the single greatest predictor of infection in patients with cancer. Three key factors are important in predicting the potential of a patient to experience an infectious episode when myelosuppressed. These factors include: 1) the degree of neutropenia, i.e., the lower the neutrophil count the more likely the patient will become infected, 2) the duration of the neutropenia, i.e., the longer a patient is neutropenic, the greater the likelihood of infection, and 3) the rate at which neutropenia develops the greater the risk of infection.

Bacterial infections in cancer patients develop quickly, especially in the neutropenic patient, and account for 85–90% of the microorganisms associated with neutropenia accompanied by fever. The most serious episodes occur from infections attributed to such gram-negative organisms as *Enterobacteriaceae* or *Pseudomonas aeruginosa*. However, infections from such gram-positive organisms as *Staphylococcus, Streptococcus, Corynebacteria*, and *Clostridia* have increased in the 1990s, probably due to the increased use of implanted central venous catheters and prophylactic antibiotics (to which these organisms develop an immunity). Listeriosis, a severe bacterial infection caused by *Listeria monocytogenes*, is another infection on the increase in cancer patients. Listeriosis has become a common complication of bone marrow transplantation in the early 2000s as well as a frequent cause of patient death.

Other organisms that cause infections in the immunocompromised cancer patient include such herpesviruses as **herpes simplex** virus 1 and 2 (HSV-1, HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV), and **Epstein-Barr virus** (EBV). Sources of secondary infections include the fungus *Candida albicans*. Common causes of secondary infection in severely immunosuppressed patients include CMV and the filamentous fungus *Aspergillus*. Aspergillosis is an increasingly common and often fatal infection in patients with hematologic cancers.

The incidence of sepsis and septic shock increases when the patient remains neutropenic for longer than seven days. Other factors that put the cancer patient at high risk for the development of sepsis include infection with a gram-negative organism, presence of a central venous catheter, history of prior infection, malnutrition, history of frequent hospitalization, increased age of patient, and concurrent (at the same time) presence of such other diseases as diabetes, cardiovascular, gastrointestinal, hepatic, pulmonary, and/or renal disease. Sites of infection that most often lead to sepsis include infection of the lungs, invasive lines, and urinary tract.

Sepsis manifests (develops) with both local and systemic symptoms that involve the neurologic, endocrine, immunologic, and cardiovascular systems. Signs of sepsis and septic shock include changes in blood pressure, heart rate and respiratory rate, among others. If left untreated, the patient can progress to septic shock which may result in death even if the shock episode is treated. Factors that appear to increase the patient's chances of survival include rapid admission to an intensive care unit and aggressive treatment with antibiotics.

Prevention

Strategies that can be used to prevent or minimize infection in the neutropenic patient include:

- Identification of patients at highest risk for infection.
- Avoiding practices by health care team members that increase colonization of microorganisms.
- Implementation of fewer invasive procedures when possible.

Cancer patients at risk for neutropenia may also benefit from treatment with two new hematopoietic growth factors, pegfilgrastim (Neulasta) and darbepoietin alfa (Aranesp). These drugs appear to be effective in reducing the risk of opportunistic infections in cancer patients as well as improving their overall quality of life.

Specific interventions in the hospital setting that can be used to prevent or minimize infection include:

- scrupulous handwashing by patient, staff, and visitors.
- good personal hygiene, including an oral care protocol by the patient.
- ambulation (movement).
- aggressive efforts to promote lung expansion.
- elimination of uncooked fruits and vegetables from the diet.
- removal of plants and other sources of stagnant water from the patient's room.
- screening and minimizing outside visitors to avoid those with infection

In addition, the hospitalized patient is assessed by the staff at least every four hours and laboratory results

are collected and analyzed to determine risk for and presence of neutropenia.

A newer method to prevent infection in the cancer patient works by decreasing the duration of neutropenia. This method decreases the period of maximum risk for infection by using hematopoietic growth factors (HGFs). These growth factors are administered daily beginning 24 hours after chemotherapy, and shorten the duration and severity of neutropenia. Therefore, the period of risk for infection is shortened. HGFs work by activating the production and maturation of RBCs, WBCs, and platelet cell lines. Specific HGFs stimulate the production and maturation of aggressive neutrophils and macrophages, which are effective in destroying pathogens (bacteria or viruses that cause infection or disease).

Sepsis can be avoided by preventing infection in immunocompromised patients and by recognizing risk factors and altering those factors whenever possible.

Treatment

Empiric antibiotic therapy is the mainstay of treatment for infection in the cancer patient. Empiric therapy refers to initiation of antibiotic therapy prior to the identification of the infecting organism. Broad-spectrum antibiotics, antibiotics effective against both gram-negative and gram-positive organisms, are administered. Commonly used agents include aminoglycosides, fluoroquinolones, glycopeptides, and beta-lactams such as penicillins, cephalosporins, carbapenems, and monobactams. Empiric **antifungal therapy** is initiated five to seven days after empiric antibiotic therapy has been started if the patient remains febrile (with a fever). Antiviral agents may be administered if there is evidence of a viral infection. The Infectious Diseases Society of America recommends a minimum of five to seven days further treatment with parenteral (introduced in other ways than intestinal absorption) antibiotic therapy after the fever resolves (returns to normal). Continued monitoring of bacterial and fungal culture results is essential. This allows the use of more tailored antibiotics for the specific infectious agents.

The neutropenic patient with fever can progress quickly to sepsis and septic shock if left untreated. The patient may also progress to septic shock if empiric antibiotic coverage is inadequate. The most common cause of septic shock in cancer patients is infection with gram-negative bacteria. The management of sepsis and septic shock is considered an emergency situation and includes treatment with broad-spectrum antibacterial coverage and maintenance of ventilation, oxygenation, fluid volume, and cardiac output.

See also Vascular access.

KEY TERMS

Corticosteroids—Adrenal cortex steroids.

Central venous catheters—Devices used for access to the blood stream. The distal tip of the catheter after insertion is located in the superior vena cava, or above the junction of the right atrium. May be used for blood sampling and for the infusion of any type of fluids, medications, nutritional supplements, and blood components.

Gram-negative—Types of bacteria that do not retain Gram stain.

Gram-positive—Types of bacteria that retain Gram stain.

Neutropenia—A decrease in the number of neutrophils (a type of white blood cell) in the blood.

Opportunistic infections—Infections caused by organisms that do not ordinarily produce disease in persons with normally functioning immune systems. Cancer patients are often susceptible to opportunistic infections.

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American College of Epidemiology. 1500 Sunday Drive, Suite 102, Raleigh, NC 27607. (919) 861-5573. <http://www.acepidemiology.org>.

American Public Health Association (APHA). 800 I Street NW, Washington, DC 20001-3710. (202) 777-APHA. <http://www.apha.org>.

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Infertility *see* **Fertility issues**

Intensity modulated radiation therapy

Definition

Intensity modulated **radiation therapy** uses a computer to deliver precise, three-dimensional doses of **x rays** to a tumor to treat cancer.

Purpose

As a new and special form of radiation therapy, intensity modulated radiation therapy (IMRT) offers special treatment options for cancer patients. When a patient has cancer, he or she may have radiation therapy to destroy the tumor or cancerous cells. The radiation therapy may be the only treatment given or a treatment prescribed along with surgery and/or **chemotherapy**.

The radiation aimed at the cancerous cells also can destroy nearby healthy cells. IMRT is an advanced treatment method that allows physicians to target the cancer so effectively that healthy tissue receives little to no radiation, even when the tumor is wrapped around a vital organ. This makes IMRT a good choice for many cancer patients, particularly those with small tumors, brain and spinal cord tumors, **prostate cancer**, cancer of the head and neck, many children, infants with certain muscle tumors, and some patients who have previously received radiation treatments. Research continues on expanding use of IMRT for a number of cancers; **clinical trials** are underway around the world.

Precautions

Any time a patient is considered for radiation therapy, physicians weigh the risks and benefits of the procedure. IMRT, like any external radiation therapy procedure, introduces x rays (ionizing radiation) to the patient's skin, tissues, and organs near the treatment area. Some patients will not be candidates for treatment. IMRT will require frequent trips to the radiation oncology facility for the prescribed treatment plan and careful following of instructions to deal with radiation side effects. On the positive side, the accuracy of IMRT means some patients who may not have been candidates for radiation therapy under older, less precise methods now can have radiation treatment. IMRT can deliver radiation to the intended target more precisely and do a better job of sparing surrounding organs and tissues. The oncology treatment team should discuss all risks and benefits of IMRT with the patient.

Description

Physicians have used radiation to treat cancer for more than 100 years. The damaging effects of x rays can destroy cancerous cells in the body and help rid the patient of the pain or related spread and complications of some cancers. For some patients, radiation therapy is the first treatment physicians choose; for others the treatment is used after surgery or chemotherapy or at the same time as chemotherapy. Radiation therapy also sometimes is called "radiotherapy."

The goal of radiation therapy is to destroy as many cancer cells as possible, while limiting damage to nearby healthy tissue. To accomplish this, complicated dose measurements are made based on information gathered by studying the tumor before radiation treatment begins. Today, physicians can use procedures such as **computed tomography** (CT) to produce three-dimensional models that can better pinpoint the tumor. Planning radiation treatments in three dimensions allows physicians to target the radiation beams at the tumor's height, width, and depth. This newer technique is called "3-D conformal radiation therapy."

IMRT is a new type of 3-D conformal radiation therapy that uses beams of varying intensities. By doing so, the beams, which can strike the tumor from three dimensions, also can deliver different doses to small areas of tissue at once. This offers more individualized targeting

of the tumor than in the past, so that the radiation oncologist (a physician who specializes in using radiation to treat cancer) can plan higher doses to the tumor and lower doses to the nearby tissue. Insurance companies have found IMRT a valuable treatment for many cancers in recent years because of its effectiveness.

Tomotherapy is a form of IMRT that delivers the radiation dose by rotating the beams over a small slice of tissue.

Most IMRT procedures are performed at a cancer center, radiation oncology physician office or outpatient facility, or in a hospital. The radiation oncologist oversees the patient's plan, working closely with a team of professionals. A medical physicist has special training in radiation physics and the operation and repair of radiology and radiation therapy equipment. The physicist also may help develop the patient's treatment plan. A medical dosimetrist works under the direction of the radiation oncologist and medical physicist to calculate radiation dose. IMRT treatments normally are performed by a radiation therapist, a specially trained technologist who positions the patient and runs the equipment. A radiation oncology nurse also may help with managing care, side effects, and explaining the treatments.

As the treatment begins, the patient is positioned on a treatment table in a precise location that has been set in treatment planning or simulation sessions. A special molding or other device may be applied to help keep the patient from moving during the procedure. The radiation therapist can observe the patient throughout the entire procedure through a window or closed circuit television. The therapist may reposition the patient during the procedure. A treatment session usually lasts about 15 to 30 minutes. The procedure should be painless, but if the patient is uncomfortable, the therapist can stop the machine. The number of treatments a patient must return for will depend on the type and stage of cancer. Some patients may receive treatments every day for a period of a several weeks.

Preparation

Before beginning IMRT treatment, the radiation oncologist and treatment team will need to know the precise location of the tumor in the body (anatomical position). This means the patient may have to go for several **imaging studies** in addition to those already completed to diagnose the cancer. Computed tomography (CT), **positron emission tomography** (PET) scans, and **magnetic resonance imaging** (MRI) may be used to provide three-dimensional information for the IMRT system. These imaging visits and the resulting work of the treatment team often are called treatment simulation. The patient also may have to go to the radiation therapy facility prior to treatment for a planning session. At this session, a special device may be molded to help the patient maintain an exact treatment position. The patient also may receive a mark or tattoo with colored ink to help align and target the equipment once treatment begins.

KEY TERMS

Ionizing radiation—Energy that is strong enough to remove an electron from an atom. It is used for diagnostic x rays and for radiation therapy.

Recur, recurrence—This refers to cancer that happens again after time has passed.

Aftercare

The radiation oncologist, radiation therapist, or radiation oncology nurse will provide instructions on IMRT aftercare. Since some effects of radiation therapy do not begin to show up until after several treatments, these instructions may vary throughout the course of treatment. Some side effects of radiation therapy occur soon after treatment begins, but others occur later. The most common side effects of external radiation therapy are **fatigue** and skin changes.

People undergoing radiation therapy who become fatigued may need to reduce their routines somewhat and not try to do too much. It is best to keep in touch with the treatment team for advice on feelings of fatigue and care for its effects. If skin becomes irritated, it also is important to follow the team's instructions concerning washing, sun exposure, and use of skin care products.

Risks

Radiation therapy carries the risk of radiation reaching and damaging normal tissues or organs near the area being targeted. However, IMRT treatment is more precise than other external radiation therapy procedures. There also is a small risk of dose being calculated incorrectly and a patient receiving too much radiation, but equipment should be run by FDA-approved software. Facilities have many quality processes in place to ensure the correct dose is given to the precise location on the correct patient. Radiation therapy also can cause low levels of white blood cells and platelets. White blood cells help fight infection and platelets help blood clot. Radiation therapy causes other side effects and risks, depending on the area being treated, though many only last a short time. For example, radiation treatment to the head

QUESTIONS TO ASK YOUR DOCTOR

- How long will my treatment last: how many times will I have to come in?
- How experienced are you and your staff in providing IMRT?
- What are some of the side effects I can expect from IMRT?
- Are there signs I should watch for following treatment that are abnormal and require a call to you or your nurse?

can cause hair loss (**alopecia**), but the hair eventually will grow back.

Normal results

After completion of IMRT treatments, cancer cells should stop dividing and growing, which should slow tumor growth. Often, cancer cells completely die and a tumor shrinks or disappears. With IMRT, there should be little radiation damage to the normal, healthy tissues around the tumor and fewer resulting side effects.

Abnormal results

The treatment may not always completely eliminate cancer cells. A cancer may still partially remain or recur at a later date. Physicians usually follow up with imaging studies to see how the treatment is progressing and set up a future schedule check for cancer recurrence.

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ORGANIZATIONS

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Teresa G. Odle

Interferons

Definition

Interferons are small, natural or synthetic protein and glycoprotein cytokines that are produced by leucocytes, T-lymphocytes, and fibroblasts in response to infection and other biological stimuli. In cancer treatment, they are used as immunotherapy against the proliferation of cancer cells.

Purpose

The goal of interferon use is to activate tumor-specific cytotoxic T-lymphocytes. T-lymphocytes are cells of the immune system that destroy foreign cells. Thus, tumor cells would be destroyed based on immunotherapy.

Description

Interferons attach to special receptors on the surface of cell membranes. They have a variety of functions, including enhancing or inhibiting enzymes, decreasing cell proliferation, or enhancing the activity of macrophages and T-lymphocytes. There are several different classes of interferons, including alpha, beta, gamma, tau, and omega. The classes can be further broken into subclasses and classified using Arabic numerals and letters. Cancer therapy research primarily focuses on alpha interferons.

In 1957, researchers discovered that the immune system produced a substance in response to a viral infection that acted as an anti-viral agent. They called that substance "interferon." Since then, recombinant DNA technology has provided a larger supply of interferons and has allowed extensive research regarding interferon's therapeutic properties against cancer.

Alpha interferons are used to treat cancers such as **hairy cell leukemia**, malignant **melanoma**, and Kaposi's sarcoma (an AIDS-related cancer). Off the label,

alpha interferons are used to treat many other cancers including **bladder cancer**, **chronic myelocytic leukemia**, kidney cancer, carcinoid tumors, non-Hodgkin's lymphoma, **ovarian cancer**, and skin cancers. Alpha interferons can be combined with other chemotherapeutic drugs such as **doxorubicin**.

In the United States, alpha interferons are sold under the brand names Roferon-A (Interferon Alfa-2a, recombinant) and Intron A (Interferon Alfa-2b, recombinant). There are no generic forms of these drugs.

Recommended dosage

Alpha interferons are only available by prescription and are given parenterally. A physician will determine dosage based on several factors such as what type of cancer is being treated, the patient's weight, and what other types of medications the patient is taking. Therefore, the dose will vary from patient to patient.

Patients can inject this drug themselves. Their physicians may recommend that they drink extra water to avoid low blood pressure while on this medication. Since this drug can have flu-like side effects, it is recommended that patients inject the drug prior to bedtime so that they are sleeping during the worst part of the side effects.

Precautions

Alpha interferons have not been shown to cause problems in the fetus of pregnant women. Because it is not known whether this drug can cross over into breast milk, it is not recommended for use in women who are breast-feeding. Before this drug is given, patients should notify their doctors if they are allergic to immunoglobulins or egg whites.

There are several medical conditions that should be considered prior to deciding whether to use alpha interferons. There can be an increase in the following disorders: bleeding problems, mental problems, convulsions, diabetes mellitus, heart attack, heart disease, liver disease, kidney disease, and lung disease. People with an overactive immune system could also have this disorder exacerbated when using alpha interferons.

Caution should be taken when using alpha interferons because they can depress the number of white blood cells. This can make patients more susceptible to infection. Therefore, they should avoid contact with others who have infections and should contact their physicians immediately if they think they are developing an infection. Patients should take care not to cut themselves, should not touch their eyes or inside of their noses with unwashed hands, and should take care when brushing their teeth so as not to cause bleeding.

KEY TERMS

Cytokines—Molecules released by cells to regulate the length and intensity of an immune response and to mediate intercellular communication.

Glycoprotein—A protein that has a carbohydrate group attached.

Immunotherapy—Treating cancer using molecules that are intended to stimulate the patient's own immune system to fight the disease.

Macrophages—A type of white blood cell that produces antibodies and molecules for cell-to-cell immune responses.

Parenteral—Medications that are administered by some means other than through the gastrointestinal tract, including through intravenous, subcutaneous, or intramuscular injection.

T-lymphocytes—A part of the immune system that fights foreign cells.

The effects of alcohol can be exaggerated while taking alpha interferons. Alcohol should only be used by permission from a physician.

Side effects

Alpha interferons can have side effects that range from minor and irritating to major and severe, needing immediate attention. Some of the less serious side effects are muscle aches, unusual metallic taste in the mouth, **fever** and chills, and general flu-like symptoms such as headache, loss of appetite (anorexia), **nausea and vomiting**, and fatigue. To reduce the flu-like symptoms physicians may suggest that the patient take acetaminophen (e.g., Tylenol) before each dosage.

Other side effects may need medical attention. Any changes with the central nervous system such as confusion, trouble thinking and focusing, mental **depression**, nervousness, or numbness or tingling of fingers, toes and face require immediate medical attention.

The side effects are dependent on the dose. As a result, the physician may modify the dose if the side effects are severe.

Interactions

Alpha interferons can interact with several different drugs, increasing their effects. Most drugs that interact

with alpha interferons are those used with disorders of the central nervous system. Some of the depressants include antihistamines, sedatives, tranquilizers, sleeping medications, prescription pain medicines, seizure medications, muscle relaxants, narcotics, and barbiturates. Prior to treatment, the doctor should be notified if the patient is taking any of these medications because this could impact the dosage prescribed.

Sally C. McFarlane-Parrott

Interleukin 2

Definition

Interleukin-2 (IL2) is a protein produced naturally in the body in very small amounts. It is produced by a type of white blood cell called a T-lymphocyte and acts as part of the immune system by helping white blood cells work. **Aldesleukin** is a biological response modifier, a synthetic form of interleukin-2.

Purpose

Interleukin-2 (IL-2) is a naturally occurring chemical, called a cytokine, produced by certain cells of the immune system. It is also manufactured and administered as a drug to augment immune responses. While it is approved by the U.S. Food and Drug Administration (FDA) only for the treatment of **kidney cancer**, it is, as of 2005, also used in the treatment of HIV and AIDS. Inhaled interleukin-2 may halt disease progression in patients with kidney cancer that has spread to the lungs. Aldesleukin, a synthetic version of interleukin-2, is used to treat cancer of the kidney and skin cancer that has spread to other parts of the body.

Aldesleukin is approved by the United States Food and Drug Administration (FDA) for treatment of metastatic malignant **melanoma** (skin cancer that has spread to other parts of the body) and metastatic renal cell **carcinoma** (kidney cancer that has spread to other parts of the body). It has also been used in combination with other drugs in treatment of AIDS and **cutaneous t-cell lymphoma**.

Description

The kidneys are a pair of bean-shaped organs, located on the sides of the spine. The kidneys filter the blood and eliminate waste in the urine through a complex system of filtration tubules. All of the blood in the body passes through the kidneys approximately twenty times an hour. Renal cell cancer (RCC) is an uncommon form of cancer that is most often characterized by the presence of cancer cells in the lining of the filtration tubules of the kidney. Advanced (metastatic) RCC refers to cancer that has spread outside the kidneys to other locations in the body. The only agent approved for metastatic RCC is high-dose Proleukin (interleukin-2). One site of cancer spread in metastatic RCC is the lungs, referred to as pulmonary **metastasis**.

Recommended dosage

IL-2 is usually administered by injection into a vein but can also be injected under the skin (subcutaneous injection). It can be given in a hospital or clinic setting by a healthcare professional and is sometimes given at home. The dosage depends on the height and weight of the patient. It is given as an infusion for 15 minutes every eight hours for up to five days followed by nine days without the drug and then another five-day cycle of infusion. Up to four subsequent maintenance cycles of IL-2 can be given with four-week intervals without the drug to patients who have responded favorably to the treatment. About 15% of patients respond to treatment. It is difficult to estimate the cost of IL-2 treatment since the dose and number of treatment cycles given varies according to patients' individual responses; however, the cost is quite high, perhaps as much as $2,000 for one cycle. A six-cycle regimen of IL-2 may cost about $14,100. Because of the high cost and low effectiveness of interleukin-2, it is often not covered by insurance plans, especially HMOs. It is covered by Medicare if given in a hospital.

Precautions

IL-2 is highly toxic and usually makes patients feel generally unwell. Any side effects should be reported to a physician, but the course of medicine should continue even though the patient feels ill, unless the physician or healthcare professional tells the patient to stop. While using aldesleukin, IL-2 patients will be more susceptible to infection. They should avoid people with colds, flu, and bronchitis. They should not have any vaccinations without their IL-2 prescriber's approval, and they should avoid anyone who has recently had an oral polio vaccine. Patients should drink several glasses of water a day to help reduce possible kidney problems.

Aldesleukin should not be used by lactating mothers. It should also be avoided in patients with the following conditions:

- acute s-t elevation myocardial infarction
- angina pectoris

- atrial fibrillation
- bacterial infection
- bradycardia
- capillary leak syndrome
- coma
- epilepsy
- fungal infections
- impaired cognition
- intestinal perforation
- ischemic bowel disease
- neoplasm metastatic to the central nervous system
- organ transplantation
- pericardial tamponade
- protozoal infection
- pulmonary disease
- renal failure
- supraventricular tachycardia
- toxic psychosis
- ventricular tachycardia
- viral infection

According to <medscape.com>, the drug should be avoided or used with extreme care in patients with the following:

- arthritis
- bone marrow depression
- bullous pemphigoid
- cerebral arteritis
- cholecystitis
- Crohn's disease
- diabetes mellitus
- disease of liver
- glomerulonephritis
- myasthenia gravis
- psychotic disorder
- renal disease
- scleroderma thyroiditis
- untreated hypothyroidism

According to <MedlinePlus.com>, the drug should be avoided by people who have the following conditions:

- chicken pox (including recent exposure)
- herpes zoster (shingles)
- heart disease
- immune system problems
- liver disease
- lung disease
- psoriasis
- underactive thyroid
- infection
- kidney disease
- mental problems
- history of seizures

Side effects

When IL-2 is given by intravenous infusion, the most common side effect is called capillary leak syndrome. This condition causes weight gain, swelling, low blood pressure, and other problems. At lower doses, people taking IL-2 get flu-like symptoms, including **fever** and muscle aches. Because IL-2 stimulates the immune system, it can make some immune disorders get worse, including arthritis, psoriasis, and diabetes. It can also reduce the number of neutrophils, a particular type of infection-fighting cell, and can cause low levels of thyroid.

When IL-2 is given by subcutaneous injection, the side effects are usually milder than with intravenous infusions. There is the added side effect of irritation at the site of the injection. Side effects show up from two to six hours after injection of IL-2 and disappear quickly after the end of each cycle. IL-2 can cause mood changes, including irritability, insomnia, confusion, or depression. These can continue for several days after IL-2 is stopped.

Interleukin-2 has a number of other side effects. More common ones are fever or chills, shortness of breath, agitation, confusion, **diarrhea**, dizziness, drowsiness, mental depression, **nausea and vomiting**, sores in the mouth and on the lips, tingling of hands or feet, unusual decrease in urination, unusual tiredness, a weight gain of five to ten pounds or more, **anemia**, heart problems, kidney problems, liver problems, low blood pressure, low platelet counts in blood, low white blood cell counts, other blood problems, under active thyroid, dry skin, loss of appetite, skin rash or redness with burning or **itching** followed by peeling, and an unusual feeling of general discomfort or illness.

Less common problems include black and tarry stools, skin blisters, blood in the urine, bloody vomit, chest pain, cough or hoarseness, lower back or side pain, painful or difficult urination, pinpoint red spots on the

KEY TERMS

Cytokine—A protein secreted by cells of the lymph system that affects the activity of other cells and is important in controlling inflammatory responses. Interleukin-2 is a cytokine.

Metastatic—Spreading from one part of the body to another.

Neutrophil—The most common type of white blood cell in humans, responsible for protecting the body against infection.

Subcutaneous—Under the skin.

T-lymphocyte—A cell in the lymphatic system that contributes to immunity by directly attacking foreign bodies, such as viruses and bacteria.

skin, severe stomach pain, unusual bleeding or bruising, bloating and mild stomach pain, blurred or double vision, faintness, fast or irregular heartbeat, loss of taste, rapid breathing, redness, swelling, and soreness of the tongue, trouble in speaking, yellow eyes and skin, constipation, headache, joint pain, and muscle pain.

Rare problems include changes in menstrual periods, clumsiness, coldness, convulsions, listlessness, muscle aches, pain or redness at site of injection, sudden inability to move, swelling in the front of the neck, swelling of the feet or lower legs, and weakness.

Interactions

Interleukin-2 can adversely interact with the anticancer drug **dacarbazine** and hormones such as prednisone or cortisone.

Ken R. Wells

Intimacy *see* **Sexuality**

Intraocular melanoma *see* **Melanoma**

Intravenous urography

Definition

Intravenous urography is a test that x rays the urinary system using intravenous dye for diagnostic purposes.

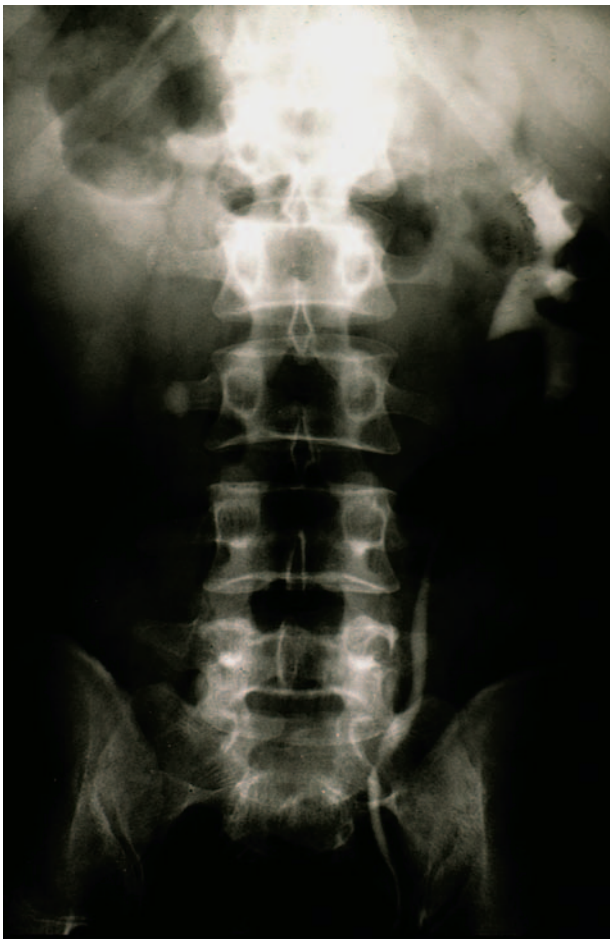
The kidneys excrete the dye into the urine. X rays can then create pictures of every structure (kidney, renal pelvis, ureter, bladder, urethra) through which the urine passes.

The procedure has several variations and many names:

- Intravenous pyelography (IVP)
- Urography
- Excretory urography
- Pyelography
- Antegrade pyelography differentiates this procedure from "retrograde pyelography," which injects dye into the lower end of the system, therefore flowing backward or "retrograde." Retrograde pyelography is better able to define problems in the lower parts of the system and is the only way to get x rays if the kidneys are not working well.
- Nephrotomography is somewhat different in that the x rays are taken by a moving **x ray** source onto a film moving in the opposite direction. By accurately coordinating the movement, all but a single plane of tissue is blurred, and that plane is seen without overlying shadows.

Every method available gives good pictures of this system, and the question becomes one of choosing among many excellent alternatives. Each condition has special requirements, while each technique has distinctive benefits and drawbacks.

- Nuclear medicine scans rely on the radiation given off by certain atoms. Chemicals containing such atoms are injected into the bloodstream. They reach the kidneys, where images are constructed by measuring the radiation emitted. The radiation is no more dangerous than standard x rays. The images require considerable training to interpret, but unique information (e.g. blood flow, kidney function, etc.) is often available using this technology. Different chemicals can concentrate the radiation in different types of tissue. This technique may require several days for the chemical to concentrate at its destination. It also requires a special detector to create the image.
- Ultrasound is a quick, safe, simple, and inexpensive way to obtain views of internal organs. Although less detailed than other methods, it may be sufficient, especially to detect obstructions.
- Retrograde pyelography is better able to define problems in the lower parts of the system and is the only way to get x rays if the kidneys are not working well. Dye is usually injected through an instrument (cystoscope) passed into the bladder through the urethra.



Intravenous urography showing contrast in distal ureter. Ureter is the narrow tube shown at the lower right of the image, and the dye has traveled from the kidney (above) and is traveling to the bladder. *(Custom Medical Stock Photo. Reproduced by permission.)*

- A **computed tomography** scan (CT or CAT scanning) uses the same kind of radiation used in x rays, but it collects information by computer in such a way that three dimensional images can be constructed, eliminating interference from nearby structures. CT scanning requires a special apparatus, but often gives better information on masses within the kidney.
- Magnetic resonance imaging (MRI) uses magnetic fields and radio frequency signals, instead of ionizing radiation, to create computerized images. This form of energy is entirely safe as long as the patient does not have any implanted metal such as artificial joints, aneurysm clips, etc. The technique is far more versatile than CT scanning as it can not only demonstrate masses, but also look at the blood vessels. However, MRI requires special apparatus and, because of the powerful magnets needed, even a special, separate building. It is quite expensive and only occasionally is this degree of detail required.

Purpose

IVP will provide information concerning most diseases of the kidneys, ureters, and bladder. The procedure is comprised of two phases. First, it requires a functioning kidney to filter the dye out of the blood into the urine. The time required for the dye to appear on x rays correlates accurately with kidney function. The second phase gives detailed anatomical images of the urinary tract. Within the first few minutes the dye "lights up" the kidneys, a phase called the nephrogram. Subsequent pictures follow the dye down the ureters and into the bladder. A final film taken after urinating reveals how well the bladder empties.

IVPs are most often done to assess structural abnormalities or obstruction to urine flow. If kidney function is at issue, more films are taken sooner to catch the earliest phase of the process.

- Stones, tumors and congenital malformations account for many of the findings.
- Kidney cysts and cancers can be seen.
- Displacement of a kidney or ureter suggests a space-occupying lesion (like a cancer of the colon, rectum, or gynecological organs) pushing it out of the way.
- Bad valves where the ureters enter the bladder will often show up.
- Bladder cancers and other abnormalities are often outlined by the dye in the bladder.
- An enlarged prostate gland will show up as incomplete bladder emptying and a bump at the bottom of the bladder.

Precautions

The only serious complication of an IVP is allergy to the iodine-containing dye that is used. Such an allergy is rare, but it can be dramatic and even lethal. Emergency measures taken immediately are usually effective.

Description

IVPs are usually done in the morning. In the x ray suite, the patient undresses and lies down. There are two methods of injecting the dye. An intravenous line can be established, through which the dye is consistently fed through the body during the procedure. The other method is to give the dye all at once through a needle that is immediately withdrawn. X rays are taken until the dye has reached the bladder, an interval of half an hour or less. The patient is asked to empty the bladder before

KEY TERMS

Contrast agent—Any substance that causes shadows on x rays; also known as contrast dye or medium.

Intravenous—Into a vein.

QUESTIONS TO ASK THE DOCTOR

- What should I feel when I am being imaged?
- Why do you recommend intravenous urography rather than another imaging technique?

one last x ray. A compression device (a wide belt containing 2 balloons that can be inflated) may be used to keep the contrast material in the kidneys. The patient needs to urinate after the compression device is removed. Another picture is taken after the bladder is emptied to see how empty the bladder is.

In the past, of the many ways to obtain images of the urinary system, the intravenous injection of a contrast agent has been considered the best. Recent studies are showing, however, that while intravenous urography is a useful technique, there may be other imaging techniques, such as B mode ultrasound, Doppler ultrasound, renal scintigraphy with angiotensin-converting enzyme inhibitors, intra-venous and intra-arterial catheter **angiography**, computed tomographic angiography, and magnetic resonance angiography, that are better or less costly.

Preparation

Emptying the bowel with **laxatives** or enemas prevents bowel shadows from obscuring the details of the urinary system. An empty stomach prevents the complication of vomiting, a rare effect of the contrast agent. Therefore, the night before the IVP the patient is asked to evacuate the bowels and to drink sparingly.

Preparation for infants and children depends on the age of the infant or child.

Aftercare

Feeling weak, nauseous, and/or lightheaded for a short time after the procedure is a possibility.

Risks

Allergy to the contrast agent is the only risk. Anyone with a possible iodine allergy, a previous reaction to x ray dye, or an allergy to shellfish must be particularly careful to inform the x ray personnel.

Exposure to x ray radiation should be noted. Most experts agree that the risk of exposure to low radiation is low compared to the benefits. Pregnant women and children are more sensitive to the risks of x rays.

Normal results

X-ray images of the kidney and bladder structures appear normal.

Abnormal results

An abnormal intravenous urography result may indicate kidney disease, birth defect, tumor, kidney stone, and/or inflammation caused by infections.

Resources

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American Cancer Society (National Headquarters). 1599 Clifton Road, N.E., Atlanta, GA 30329. (800) 227-2345. <http://www.cancer.org>.

Cancer Research Institute (National Headquarters). 681 Fifth Avenue, New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

Kidney Cancer Association. 1234 Sherman Avenue, Suite 203, Evanston, IL 60202-1375. (800) 850-9132. <http://www.kidneycancerassociation.org>.

National Cancer Institute. 9000 Rockville Pike, Building 31, Room 10A16, Bethesda, MD 20892. (800) 422-6237. <http://www.nci.nih.gov>.

National Kidney Cancer Association. 1234 Sherman Avenue, Suite 203, Evanston, IL 60202-1375. (800) 850-9132.

National Kidney Foundation. 30 East 33rd Street, New York, NY 10016. (800) 622-9010. <http://www.kidney.org>.

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Investigational drugs

Definition

"Investigational drugs" refers to drugs that have received FDA approval for human testing, including those drugs still undergoing **clinical trials**, but are not approved for marketing to the general public.

Description

Investigational drugs represent interesting and novel new agents in the fight against cancer. These agents include **chemotherapy** designed to treat specific cancers, to provide palliative therapy for pain and symptoms, and to reduce invasive cancers in high-risk patients. The challenge faced by private and commercial investigators is to reduce the lag time in bringing an investigational drug to market without compromising drug quality or patient safety. The guidelines that insure the correct procedures are being followed in the process of drug development and approval fall under the direction of the Food and Drug Administration (FDA).

At present, the cycle of investigational drug research and development, to clinical trials, to FDA approval can easily cover a period of 10-12 years. Under exceptional circumstances, provisions can be made for patient use of investigational drugs under the guidance of specially trained and registered oncologists. These specific investigational drugs are classified as "Group C" drugs, and have demonstrated a high level of reproducible activity in pre-clinical testing. There is also the route of "Accelerated FDA Approval" for some investigational drugs. Accelerated approval relies on specific indicators that suggest that a particular investigational drug is likely to have beneficial effects before the benefits have been clinically verified. All investigational drugs that have been granted accelerated approval must undergo follow-up testing in order to receive final FDA approval. Some researchers are presently working on a format to combine traditional clinical testing of investigational drugs with a global database of drug information. This integrated system would give FDA monitoring agencies and healthcare providers access to the most comprehensive source of archived data available on investigational drugs. This combined approach is another attempt to reduce approval time for investigational drugs and make these agents available to the cancer patient for treatment.

Resources

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Irinotecan

Definition

Irinotecan is a drug used to treat certain types of cancer. Irinotecan, also known as CPT-11, is available under the trade name Camptosar, and may also be referred to as irinotecan hydrochloride or camptothecin-11.

Purpose

Irinotecan is an antineoplastic agent used to treat cancer. A primary use of the drug is treatment of colon or rectal cancers that have recurred or progressed while the patient was on 5-FU (fluorouracil) therapy. Irinotecan also can be given as first line therapy with 5-FU and **leucovorin** for patients with metastatic colon or **rectal cancer**. Other uses for irinotecan include treatment of small cell lung cancer, nonsmall cell lung cancer, **ovarian cancer**, stomach cancer, **breast cancer**, pancreatic cancer, leukemia, **lymphoma**, and **cervical cancer**.

Several 2003 studies showed some potential new uses for irinotecan. One reported that a combination of irinotecan and docetaxel can help patients with esophageal cancer who have been extensively pretreated with cisplatin. Weekly use of irinotecan has shown preliminary results in treating patients with nonsmall cell lung cancer with minimal side effects. Another 2003 study reported that when used in combination with cancer

drugs cisplatin and epirubicin, irinotecan might have promising broad antitumor activity. In the future, irinotecan might be used in combination therapies to treat many types of tumors.

Description

Irinotecan is a synthetic derivative of the naturally occurring compound camptothecin. Camptothecin belongs to a group of chemicals called alkaloids and is extracted from plants such as *camptotheca acuminata*. Captothecin was initially investigated as a chemotherapeutic agent due to its anti-cancer activity in laboratory studies. The chemical structure and biological action of irinotecan is similar to that of camptothecin and **topotecan**.

Irinotecan inhibits the normal functioning of the enzyme topoisomerase I. The normal role of topoisomerase I is to aid in the replication, recombination, and repair of deoxyribonucleic acid (DNA). Higher levels of topoisomerase I have been found in certain cancer tumors compared to healthy tissue. Inhibiting topoisomerase I causes DNA damage. This damage leads to apoptosis, or programmed cell death.

Recommended dosage

Patients should be carefully monitored during irinotecan treatment for toxicity. Irinotecan is given at a dose of 125 mg per square meter of body surface area per week for four weeks, followed by a two week rest period. Other dosing schedules include 100 mg per square meter of body surface area per day for three days every three weeks, or 100-115 mg per square meter of body surface area per week, or 200-350 mg per square meter of body surface area every 3 weeks. The drug is administered through the vein over a 90-minute period. The initial dose of irinotecan may be adjusted downward depending on patient tolerance to the toxic side effects of irinotecan.

Treatment may be continued as long as intolerable side effects do not develop and patients continue to benefit from the treatment.

Precautions

Irinotecan should only be used under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Special caution, especially in those 65 years and older, should be taken to monitor the toxic effects of irinotecan, particularly **diarrhea**, nausea, and vomiting. Because irinotecan is administered intravenously, the site of infusion should be monitored for signs of inflammation. Should inflammation occur, flushing the site with sterile water and applying ice are recommended. Irinotecan may cause **nausea and vomiting**, and premedication with antiemetic agents is recommended.

Neither the effects of irinotecan in patients with significant liver dysfunction nor the safety of irinotecan in children have been established. Irinotecan should not be administered to pregnant women. Women of child-bearing age are advised not to become pregnant during treatment with this drug.

KEY TERMS

Alkaloid—A nitrogen-containing compound occurring in plants.

Anorexia—Loss of appetite and the inability to eat.

Apoptosis—An active process in which a cell dies due to a chemical signal. Programmed cell death.

Diuretic—An agent that increases the amount of urine the body produces.

Inflammation—A response to injury, irritation, or illness characterized by redness, pain, swelling, and heat.

Metastatic—Spread of a disease from the organ or tissue of origin to other parts of the body.

Side effects

Early- or late-onset diarrhea are common side effects of irinotecan. Late-onset diarrhea, occurring more than 24 hours after irinotecan administration, can be life-threatening and should be treated promptly. Patients should immediately report diarrhea to their physician. Patients can also take the antidiarrheal drug loperamide as prescribed by their physician at the first sign of diarrhea. Suppression of bone marrow function is another serious side effect commonly observed in this treatment. Additional side effects, including nausea, vomiting, **anorexia** (loss of appetite), pain, **fatigue**, and hair loss (alopecia) may occur.

Interactions

Irradiation treatment during the course of irinotecan treatment is not recommended. Patients who have received prior pelvic or abdominal irradiation treatment should notify their physician. Since irinotecan may cause diarrhea, the use of **laxatives** should be avoided. The use of diuretics should be closely monitored. The adverse side effects caused by irinotecan may be increased by

other **antineoplastic agents** having similar adverse effects and should generally be avoided.

Resources

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Marc Scanio
Teresa G. Odle

Islet cell carcinoma *see* **Pancreatic cancer, endocrine**

Itching

Description

Itching, also called pruritus, is an unpleasant sensation of the skin that causes a person to scratch or rub the area to find relief. Itching can be confined to one spot (localized) or over the whole body (generalized). Severe scratching can injure the skin causing redness, bumps, and scratches. Injured skin is prone to infection.

Itching can profoundly affect quality of life. It can torment the patient and cause discomfort, stress, loss of sleep, concentration difficulty, and constant concern.

Causes

The biology underlying itching is not fully understood. It is believed that itching results from the interactions of several different chemical messengers. Although itching and pain sensations were at one time thought to be sent along the same nerve pathways, researchers reported the discovery in 2003 of itch-specific nerve pathways. Nerve endings that are specifically sensitive to itching have been named pruriceptors.

Research into itching has been helped by the recent invention of a mechanical device called the Matcher, which electrically stimulates the patient's left hand. When the intensity of the stimulation equals the intensity of itching that the patient is experiencing elsewhere in the body, the patient stops the stimulation and the device automatically records the measurement. The Matcher was found to be sensitive to immediate changes in the patient's perception of itching as well as reliable in its measurements.

Itching is associated with a variety of factors including skin diseases, blood diseases, emotions, and drug reactions as well as by cancer and cancer treatments. Itching can be a symptom of cancer including **Hodgkin's disease**, non-Hodgkin's lymphoma, leukemia, **Bowen's disease**, **multiple myeloma**, central nervous system (brain and spinal cord) tumors, **germ cell tumors**, and invasive squamous cell carcinoma. The buildup of toxins in the blood, caused by kidney, gallbladder, and liver disease, can cause itching. Cancer treatments that are associated with itching are: **radiation therapy**, **chemotherapy**, and biological response modifiers (drugs that improve the patient's immune system). Skin reactions are more severe when both chemotherapy and radiation therapy are used. Patients treated with **bone marrow transplantation** may develop itching resulting from **graft-vs.-host disease**. Itching can be caused by infection.

General medications that may be used by cancer patients can cause itching. Itching can be caused by drug reactions from **antibiotics**, **corticosteroids**, hormones, and pain relievers (analgesics).

Itching can be a sign that the patient is very sensitive to a particular chemotherapy drug. Chemotherapy drugs and biological response modifiers that can cause itching include:

- allopurinol
- aminoglutethimide
- bleomycin
- carmustine
- chlorambucil
- cyclophosphamide
- cytarabine
- daunorubicin
- doxorubicin
- hydroxyurea
- idarubicin
- interleukin (aldesleukin)
- mechlorethamine
- megestrol acetate
- mitomycin-C
- tamoxifen

- topiramate

Itching commonly occurs during radiation therapy. Parts of the body that are particularly sensitive to radiation are the underarms, groin, abdomen, breasts, buttocks, and skin around the genitals (perineum) and anus (perianal). Itching is usually caused by skin dryness when the oil (sebaceous) glands are damaged by the radiation. Radiation also causes skin darkening, redness, and skin shedding, which can all cause itching.

Itching caused by cancer usually disappears once the cancer is in remission or cured. Chemotherapy-induced itching usually disappears within 30 to 90 minutes after the drug has been administered. Itching caused by radiation therapy will resolve once the injured skin has healed.

Treatments

There are three aspects in the treatment of itching: managing the underlying cancer, maintaining skin health, and relief of itching.

Patients should avoid the particular things that cause or worsen their itching. Also, patients can take measures to maintain skin health. Suggestions include:

- taking short baths in warm water
- using mild soaps and rinsing well
- applying bath oil or moisturizing cream after bathing
- avoiding use of cosmetics, perfumes, deodorants, and starch-based powders
- avoiding wool and other harsh fabrics
- using mild laundry detergents and rinsing thoroughly
- avoiding use of dryer anti-static sheets
- wearing loose-fitting cotton clothing
- avoiding high-friction garments such as belts, pantyhose, and bras
- maintaining a cool environment with a 30% to 40% humidity level
- using cotton sheets
- avoiding vigorous exercise (if sweating causes itching)
- avoiding skin products that are scented or contain alcohol or menthol

To reduce skin injury caused by scratching the patient should keep fingernails short, wear soft cotton mittens and socks at night, and keep the hands clean. Gently rubbing the skin around the itch or applying pressure or vibration to the itchy spot may reduce itching. Using a soft infant toothbrush to gently stroke the itchy area may relieve itching. Itching may be relieved by applying a cool washcloth or ice to the itchy area.

The most effective way to relieve itching is to treat the underlying disease. Sometimes, itching disappears as soon as a tumor is treated or removed.

Itching may be relieved by applying any of a variety of different products to the skin. The patient may need to try several before the most effective one is found. The patient's physician should be consulted before any anti-itch products are used. Topical treatments include:

- Corticosteroids, such as hydrocortisone, reduce inflammation and itching.
- Calamine lotions can cool and soothe itchy skin. These products can be drying, which may be helpful for weeping or oozing rashes.
- Antihistamine creams stop itching that is associated with the chemical messenger histamine.
- Moisturizers treat dry skin which helps to relieve itching. Moisturizers that are recommended to cancer patients include brand names Alpha Keri, Aquaphor, Eucerin, Lubriderm, Nivea, Prax, and Sarna. Moisturizers should be applied after bathing and at least two or three times daily.
- Gels that contain a numbing agent (e.g. lidocaine) can be used on some parts of the body.

Itching may be treated with whole-body medications. Some of these systemic treatments include:

- antihistamines
- tricyclic antidepressants
- sedatives or tranquilizers
- such selective serotonin reputake inhibitors as paroxetine (Paxil) and sertraline (Zoloft)
- binding agents (such as cholestyramine which relieves itching associated with kidney or liver disease).
- aspirin
- cimetidine

Alternative and complementary therapies

A well-balanced diet that includes carbohydrates, fats, minerals, proteins, **vitamins**, and liquids will help to maintain skin health. Capsules that contain eicosapentaenoic acid, which is obtained from herring, mackerel, or salmon, may help to reduce itching. Vitamin A plays an important role in skin health. Vitamin E (capsules or ointment) may reduce itching. Patients should check with their treating physician before using supplements.

Homeopathy has been reported to be effective in treating systemic itching associated with hemodialysis.

KEY TERMS

Chemical messengers—Chemicals that transmit messages from one place to another.

Generalized itching—Itching that occurs over the whole body.

Histamine—A chemical messenger that can be associated with itching.

Localized itching—Itching that is confined to one spot.

Pruriceptors—Nerve endings specialized to perceive itching sensations.

Pruritus—The medical term for itching.

Baths containing oil with milk or oatmeal are effective at relieving localized itching. Evening primrose oil may soothe itching and may be as effective as corticosteroids. Calendula cream may relieve short-term itching. Other herbal treatments that have been recently reported to relieve itching include sangre de drago, a preparation made with sap from a South American tree; and a mixture of honey, olive oil, and beeswax.

Distraction, music therapy, relaxation techniques, and visualization may be useful in relieving itching. Ultraviolet light therapy may relieve itching associated with conditions of the skin, kidneys, blood, and gallbladder. There are some reports of the use of acupuncture and transcutaneous electrical nerve stimulators (TENS) to relieve itching.

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Itraconazole *see* **Antifungal therapy**

IVP, Excretory urography, Intravenous pyelography *see* **Intravenous urography**

K

Kaposi's sarcoma

Definition

Kaposi's sarcoma (KS) is a cancer of the skin, mucous membranes, and blood vessels; it is the most common form of cancer in AIDS patients. It was named for Dr. Moritz Kaposi (1837-1902), a Hungarian dermatologist who first described it in 1872. As of 2001, researchers disagree as to whether KS is a true cancer or a disorder of the skin that develops as a reaction to infection by a herpes virus.

Description

The formal medical term for Kaposi's sarcoma is multiple idiopathic hemorrhagic sarcoma. This term means that KS develops in many different sites on the patient's skin or internal organs; that its cause is unknown; and that it is characterized by bleeding. The lesions (areas of diseased or damaged skin), which are usually round or elliptical in shape and a quarter of an inch to an inch in size, derive their characteristic purple or brownish color from blood leaking out of capillaries (small blood vessels) in the skin. In KS, the capillaries begin to grow too rapidly and irregularly, which causes them to become leaky and eventually break. The lesions themselves may become enlarged and bleed, or cause the mucous membranes of the patient's internal organs to bleed.

There are three types of KS lesions, defined by their appearance:

- Nodular. These are reddish-purple, but are sometimes surrounded by a border of yellowish or brown pigment. Nodular lesions may appear to be dark brown rather than purple in patients with dark skin.
- Infiltrating. Infiltrating lesions may be large or have a raised surface. They typically grow downward under the skin.
- Lymphatic. These lesions are found in the lymph nodes and may be confused with other causes of swollen lymph nodes.

As of 2005, KS is classified into five types:

- Classic KS. This form of KS is sometimes called indolent KS because it is slow to develop. Classical KS is most commonly found in males between 50 and 70 years of age, of Italian or Eastern European Jewish descent.
- African KS. This form of the disease appears in both an indolent and an aggressive form in native populations in equatorial Africa. It accounts for almost 10% of all cancers in central Africa.
- Immunosuppressive treatment-related KS. The third form of KS occurs in kidney transplant patients who have been given drugs to suppress their immune systems-usually prednisone and **azathioprine**. This form of KS is sometimes called iatrogenic KS, which means that it is caused unintentionally by medical treatment.
- Epidemic KS. Epidemic KS was first reported in 1981 as part of the AIDS epidemic. Most cases of epidemic KS in the United States have been diagnosed in homosexual or bisexual men.
- Non-epidemic gay-related KS. This form of KS occurs in homosexual men who do not develop HIV infection. Non-epidemic gay-related KS is an indolent form of the disease that primarily affects the patient's skin.

Demographics

The demographic distribution of KS varies considerably across its five types:

- Classic KS. Classic KS is considered a rare disease, with a male/female ratio of 10:1 or 15:1. In North America and Europe, most patients are between 50 and 70 years old. Classic KS is more common in men from Mediterranean countries and in Ashkenazic Jews.
- African KS. African KS has the same male/female ratio as classic KS, although most patients with African KS are younger. A form of African KS that attacks the lymphatic system primarily affects children, with a male/female ratio of 3:1.

- Immunosuppresive treatment-related KS. This form of KS occurs mostly in kidney-transplant patients, at a rate of 150 to 200 times as often as in the general population. It represents 3% of all tumors that occur in kidney-transplant patients. The male/female ratio is 2:1.
- Epidemic KS. Epidemic KS is overwhelmingly a disease of adult homosexual or bisexual males. It is 20,000 times more common in people with AIDS than in those without HIV infection. According to the National Institutes of Health (NIH), 95% of all the cases of epidemic KS in the United States have been diagnosed in homosexual or bisexual males. Epidemic KS is far more prevalent among homosexual or bisexual males with AIDS than among hemophiliacs or intravenous drug users with AIDS. Prior to 1995, about 26% of all homosexual males with AIDS had KS as their first symptom or eventually developed KS, as compared with fewer than 3% of heterosexual intravenous drug users with AIDS. This clustering of KS cases among a subpopulation of AIDS patients led to the hypothesis that a blood factor transmitted by sexual contact is a partial cause of KS. The number of new cases of AIDS-related KS has declined in recent years, for reasons that are not yet clear. Some researchers think that the introduction of highly active antiretroviral therapy, or HAART, is related to the decline in the number of cases of epidemic KS. As of 2001, only about 12% of AIDS patients develop KS.
- Non-epidemic gay-related KS. This small group of KS patients is entirely male.

Causes and symptoms

Causes

GENETIC FACTORS The role of genetic factors in KS varies across its five types. Classic KS is the only form associated with specific ethnic groups. In addition, patients with classic KS and immunosuppressive treatment-related KS have a higher incidence of a genetically determined immune factor called HLA-DR.

MALE HORMONES The fact that all forms of KS affect men more often than women may indicate that androgens (male sex hormones) may be a factor in the development of KS.

IMMUNOSUPPRESSION In addition to organ transplant patients receiving immunosuppressive drugs, patients who are taking high-dose **corticosteroids** are also at increased risk of developing KS.

INFECTIOUS AGENTS Some researchers think that cytomegalovirus (CMV) and **human papilloma virus** (HPV) may be involved in the development of KS because fragments of these two types of virus have been found in KS tumor samples. The most likely candidate for an infectious agent, however, is human herpesvirus 8 (HHV-8), which is sometimes called KS-associated herpesvirus (KSHV). Fragments of the HHV-8 genome were first detected in 1994 by using a technique based on polymerase chain reaction (PCR) analysis. HHV-8 belongs to a group of herpesviruses called rhadinoviruses, and is the first herpesvirus of this subtype to be found in humans. HHV-8 is, however, closely related to the human herpesvirus called **Epstein-Barr virus** (EBV). EBV is known to cause infectious mononucleosis as well as tumors of the lymphatic system, and may be involved in other malignancies, including the African form of **Burkitt's lymphoma**, **Hodgkin's disease**, and **nasopharyngeal cancer**. HHV-8 has been found in tissue samples from patients with African KS, classic KS, and immunosuppression treatment-related KS as well as epidemic KS. HHV-8 is also associated with a rare noncancerous disease called Castleman's disease, which affects the lymph nodes. Some KS patients have been found to have KS and Castleman's disease occurring together in the same lymph node.

OTHER CAUSES Some practitioners of alternative medicine regard environmental toxins, psychological distress, and constitutional weaknesses as probable or partial causes of KS. These theories are discussed in more detail under the heading of alternative treatments.

Symptoms

CLASSIC KS The symptoms of classic KS include one or more reddish or purplish patches or nodules on one or both legs, often on the ankles or soles of the feet. The lesions slowly enlarge over a period of 10-15 years, with additional lesions sometimes developing. It is rare for classic KS to involve the patient's internal organs, although bleeding from the digestive tract sometimes occurs. About 34% of patients with classic KS eventually develop non-Hodgkin's lymphoma or another primary cancer.

AFRICAN KS The symptoms of the indolent form of African KS resemble those of classic KS. The aggressive form, however, produces tumors that may penetrate the tissue underneath the patient's skin, and even the underlying bone.

EPIDEMIC KS Epidemic KS has more varied presentations than the four other types of KS. Its onset is usually, though not always, marked by the appearance of widespread lesions at many different points on the patient's skin and in the mouth. Most HIV-infected patients who develop KS skin and mouth lesions feel healthy and have no systemic symptoms. On the other hand, KS may affect the patient's lymph nodes or gastrointestinal tract prior to causing skin lesions.

Patients with epidemic KS almost always develop disseminated (widely spread) disease. The illness progesses from a few localized lesions to lymph node involvement and further spread to other organs. Disseminated KS is defined by the appearance of one or more of the following: a count of 25 or more external lesions; the appearance of 10 or more new lesions per month; and the appearance of visible lesions in the patient's lungs or stomach lining.

In some cases, disseminated KS causes painful swelling (edema) of the patient's feet and lower legs. The lesions may also cause the surrounding skin to ulcerate or develop secondary infections. The spread of KS to the lungs, called pleuropulmonary KS, usually occurs at a late stage of the disease. KS involvement of the lungs causes bleeding, coughing, shortness of breath, and eventual respiratory failure. Most patients who die directly of KS die from its pleuropulmonary form.

Diagnosis

Physical examination and patient history

The diagnosis of any form of KS requires a careful examination of all areas of the patient's skin. Even though the characteristic lesions of classic KS appear most frequently on the legs, all forms of KS can produce lesions on any area of the skin. An experienced doctor, who may be a dermatologist, an internist, or a primary care physician, can make a tentative diagnosis of KS on the basis of the external appearance of the skin lesions (size, shape, color, and location on the face or body), particularly when they are accompanied by evidence of lymph node involvement, internal bleeding, and other symptoms associated with disseminated KS. The doctor may touch or press on the lesions to find out whether they turn pale (blanch); KS plaques and nodules do not blanch under fingertip pressure. In addition, KS lesions are not painful when they first appear.

Other signs of KS may appear on the soft palate or the membrane covering the eye (conjunctiva). In addition, the doctor will press on the patient's abdomen in order to detect any masses in the liver or spleen.

A thorough history is necessary in order to determine whether the patient's ethnic background, lifestyle, or medical history places him or her in a high-risk category for KS.

Biopsy

A definitive diagnosis of KS requires a skin **biopsy** in order to rule out bacillary angiomatosis, a bacterial infection resembling cat-scratch disease. It is caused by a bacillus, *Bartonella henselae*. Collecting a tissue sample for a biopsy is not difficult if the patient has skin lesions, but can be complicated if the nodules are primarily internal. An endoscopy of the upper end of the digestive tract may be performed in order to obtain a tissue sample from an internal KS lesion.

Under the microscope, an AIDS-related KS lesion will show an unusually large number of spindle-shaped cells mixed together with small capillaries. The origin of the spindle-shaped cells is still unknown. The tumor cells in a KS lesion resemble smooth muscle cells or fibroblasts, which are cells that help to form the fibers in normal connective tissue.

If the patient's lymph nodes are enlarged, a biopsy may be done in order to rule out other causes of swollen lymph nodes.

Other tests

Other diagnostic tests may be performed if the patient appears to have disseminated KS. These tests include:

- Chest x ray. A radiograph of the patient's lungs will show patchy areas of involved tissue.
- Gallium scan. The results will be negative in KS.
- Bronchoscopy. This procedure allows the doctor to examine the patient's bronchial pathways for visible KS lesions. It is not, however, useful for obtaining tissue samples for biopsy.
- Endoscopy. Examination of the patient's stomach allows the doctor to examine the mucous lining for KS lesions as well as to obtain a tissue sample.

Treatment team

KS patients may receive treatment for skin lesions from a dermatologist or radiologist as well as treatment for lung or lymphatic involvement from internists or primary care practitioners. A surgeon may be called in to remove lesions in the digestive tract if they are bleeding or blocking the passage of food. Children with KS may be treated by pediatricians or by primary care physicians who specialize in treating AIDS patients.

Clinical staging, treatments, and prognosis

Staging

The NIH recommends individualized staging of patients with classic KS, due to the age of most patients, the localized nature of the lesions, the slow progression of the disease, and the low risk of spread to the internal organs.

The criteria for staging epidemic KS have evolved over the past decade in response to changes in the treatment of HIV infection and to the recognition that KS

does not fit well into standard categories of tumor assessment. Several different systems have been used to stage epidemic KS, but none is completely satisfactory.

NYU STAGING SYSTEM One staging system that originated at New York University divides KS patients into four groups according to the following symptom clusters:

- Skin lesions that are indolent (slow-growing) and limited to relatively small areas of the body.
- Skin lesions limited to specific regions of the body but aggressive in growth. There may or may not be involvement of lymph nodes.
- General involvement of the skin and mucous membranes, with or without lymph node involvement.
- Involvement of the internal organs.

AIDS CLINICAL TRIALS GROUP (ACTG) STAGING SYSTEM The ACTG Oncology Committee published a staging system for epidemic KS in 1989. This system was reevaluated in 1995 and is undergoing continued assessment. It is based on three criteria: extent of tumor; condition of the patient's immune system; and presence of systemic illness:

- Tumor (T): Good risk (0) is a tumor limited to the skin and/or lymph nodes and/or minimal oral disease (limited to the palate). Poor risk (1) is any of the following: edema associated with the tumor; widespread KS in the mouth; KS in the digestive tract; KS in other viscera.
- Immune system (I): Good risk (0) is a CD4 cell count greater than 200 per cubic millmeter. Poor risk (1) is a CD4 cell count lower than 200 per cubic millimeter.
- Systemic illness (S): Good risk (0) is no history of opportunistic infections (OI) or **thrush**; no "B" symptoms (unexplained **fever**, **night sweats**, **diarrhea** lasting more than 2 weeks, **weight loss** greater than 10%); performance status above 70 on the Karnofsky scale. Poor risk (1) is any of the following: history of OI or thrush; presence of "B" symptoms; Karnofsky score lower than 70; and other HIV-related illnesses.

Treatment

Treatment of KS depends on the form of the disease.

CLASSIC KS **Radiation therapy** is usually quite effective if the patient has small lesions or lesions limited to a small area of skin. Low-voltage photon radiation or electron beam therapy give good results. Surgical removal of small lesions is sometimes done, but the lesions are likely to recur. The best results are obtained from surgical treatment when many small lesions are removed over a period of years.

For widespread skin disease, radiation treatment with electron beam therapy is recommended. Classic KS has not often been treated with **chemotherapy** in the United States, but some researchers report that treatment with **vinblastine** or **vincristine** has been effective. Disease that has spread to the lymph nodes or digestive tract is treated with a combination of chemotherapy and radiation treatment.

IMMUNOSUPPRESSIVE TREATMENT-RELATED KS The standard pattern of therapy for this form of KS begins with discontinuing the immunosuppressive medications if they are not essential to the patient's care. Treatment of the KS itself may include radiation therapy if the disease is limited to the skin, or single- or multiple-drug chemotherapy.

EPIDEMIC KS As of 2001, there is no cure for epidemic KS. Treatment is aimed at reducing the size of skin lesions and alleviating the discomfort of open ulcers or swollen tissue in the legs. There are no data that indicate that treatment prolongs the survival of patients with epidemic KS. In addition to treatment of the KS itself, these patients also need ongoing retroviral therapy and treatment of any opportunistic infections that may develop. An additional complication in treating epidemic KS is that highly active antiretroviral therapy, or HAART, is not the "magic bullet" that some had hoped when it was introduced in 1998. HAART uses three- or four-drug combinations to treat HIV infection. Problems with HAART include severe psychiatric as well as physical side effects, in addition to the patient's risk of developing a drug-resistant form of HIV if even one dose of medication is missed. The complex dosing schedules as well as the medication side effects make it difficult to assess the effectiveness of treatments aimed at the KS by itself.

Small KS lesions respond very well to radiation treatment. They can also be removed surgically or treated with **cryotherapy**, a technique that uses liquid nitrogen to freeze the lesion. Lesions inside the mouth (on the palate) can be treated with injections of vinblastine. In addition, the patient may be given topical alitretinoin (Panretin gel), which is applied directly to the lesions. Alitretinoin received FDA approval for treating KS in 1999.

Systemic treatments for epidemic KS consist of various combinations of anti-cancer drugs, including vincristine (Oncovin), vinblastine (Velban), **bleomycin** (Blenoxane), **doxorubicin** (Adriamycin), **daunorubicin** (DaunoXome), interferon-alpha (Intron A, Roferon-A), **etoposide** (VePesid), or **paclitaxel** (Taxol). The effectiveness of systemic treatments ranges from 50% for high-dose therapy with interferon-alpha to 80% for

combinations of vincristine, vinblastine, bleomycin, doxorubicin, and etoposide. The drawbacks of systemic treatment include the toxicity of these drugs and their many side effects. Interferon-alpha can be given only to adult patients with relatively intact immune systems and no signs of lymphatic involvement. The side effects of systemic chemotherapy include hair loss (**alopecia**), **nausea and vomiting**, **fatigue**, diarrhea, headaches, loss of appetite (anorexia), allergic reactions, back pain, abdominal pain, and increased sweating.

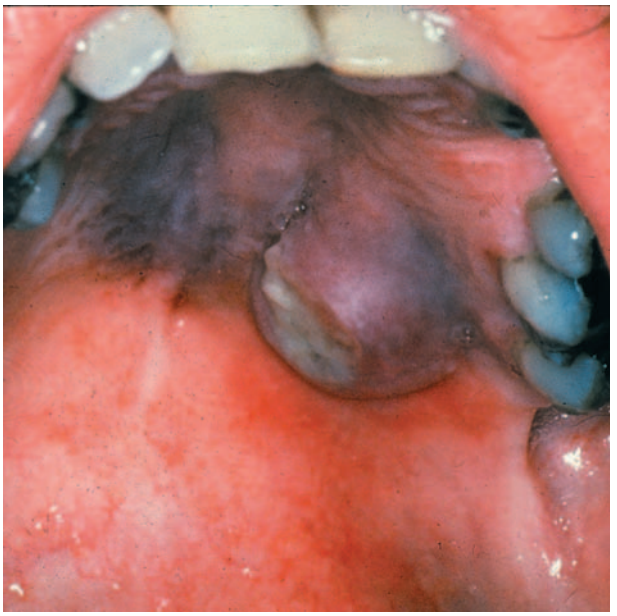
As of 2005, the standard for first-line treatment of epidemic KS is one of the FDA-approved anthracyclines such as liposomal doxorubicin (Doxil) or liposomal daunorubicin (DaunoXome), rather than a combination drug regimen. Liposomes are small sacs consisting of an outer layer of fatty substances used to coat an inner core of another medication. In addition to concentrating the drug's effects on the tumor, liposomes moderate the side effects.

In 1997, the FDA approved paclitaxel (Taxol) for epidemic KS resistant to treatment. Paclitaxel is a drug derived from the bark of the Pacific yew tree that prevents the growth of cancer cells by preventing the breakdown of normal cell structures called microtubules. After paclitaxel treatment, cancer cells become so clogged with microtubules that they cannot grow and divide. The drug has serious side effects, most notably suppression of the patient's bone marrow.

Experimental treatments for AIDS-related KS include retinoic acid, which is derived from vitamin A; and other drugs that inhibit the formation of new blood vessels (angiogenesis) in tumors. The reason for inhibiting angiogenesis is that new blood vessels keep a cancer supplied with oxygen and nutrients, which help the cancer grow and spread to other parts of the body. Antiangiogenic agents that have been proposed for treating KS include Fumagillin, SP-PG, and Platelet 4 factor. As of 2005, the effectiveness of these substances in humans is not yet known. Approval by the Food and Drug Administration will require several years after the test results are known.

Prognosis

The prognosis of KS varies depending on its form. Patients with classic KS often survive for many years after diagnosis; death is often caused by another cancer, such as non-Hodgkin's lymphoma, rather than the KS itself. The aggressive form of African KS has the poorest prognosis, with a fatality rate of 100% within three years of diagnosis. Patients with immunosuppressive treatment-related KS have variable prognoses; in many cases, however, the KS goes into remission once the immune-suppressing drug is discontinued. The prognosis of patients with epidemic KS also varies, depending on the patient's general level of health. As a rule, patients whose KS has spread to the lungs have the poorest prognosis.

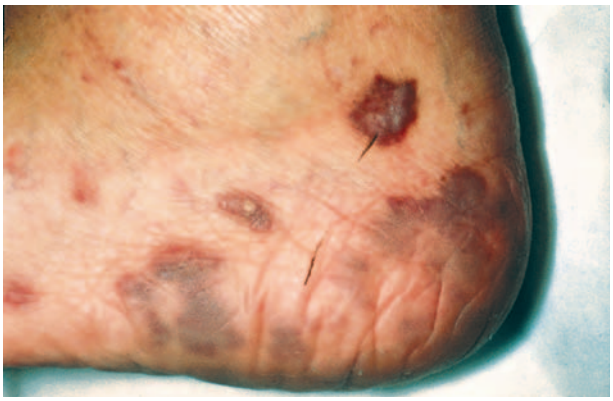


This HIV-positive patient is afflicted with Kaposi's sarcoma inside the mouth. The tumor is toward the back of the mouth, to the right. *(Custom Medical Stock Photo. Reproduced by permission.)*

Alternative and complementary therapies

SHARK CARTILAGE The only alternative treatment for epidemic KS that has been evaluated by the NIH is shark cartilage. Shark cartilage products are widely available in the United States as over-the-counter (OTC) preparations that do not require FDA approval. A 1995 review of alternative therapies found more than 40 brand names of shark cartilage products for sale in the United States to treat arthritis and psoriasis as well as KS. The cartilage can be taken by mouth or by injection.

The use of shark cartilage to treat KS derives from a popular belief that sharks and other cartilaginous fish (skates and rays) do not get cancer. This belief is countered by findings from samples of captured sharks that they do in fact develop various kinds of tumors. There are three explanations of the role of shark cartilage in preventing KS. Some researchers have proposed that it kills cancer cells directly. A second explanation is that cartilage stimulates the human immune system. The third theory, which has more evidence in its favor than the first two, is that the cartilage slows down or prevents angiogenesis. Two complex proteins in shark cartilage,



Purple-colored (violaceous) plaques of Kaposi's sarcoma on the heel and side of foot. *(Centers for Disease Control.)*

identified as U-995 and SCF2, have been shown to inhibit angiogenesis in laboratory studies. As of December 2000, only three studies using human subjects have been published; the results are inconclusive. The complete results of three other studies using shark cartilage in human subjects have not yet been published in complete form. Preliminary reports of NIH-sponsored **clinical trials** are also not yet available; however, all three studies being currently conducted have received the lowest rating (3iii) for the statistical strength of the study's design.

The side effects of treatment with shark cartilage include mild to moderate nausea, vomiting, abdominal cramps, constipation, low blood pressure, abnormally high levels of blood calcium (**hypercalcemia**), and general feelings of weakness.

OTHER ALTERNATIVE THERAPIES Other alternative treatments for KS are aimed almost completely at epidemic KS. Most are based on assumptions that AIDS victims have had their immune systems weakened by such environmental toxins as lead and radioactive materials, or by psychological stress generated by societal disapproval of homosexuality. Naturopaths would add such life-style stresses as the use of tobacco and alcohol, as well as poor sleep patterns and nutritional deficiencies. Homeopaths believe that AIDS is the product of hereditary predispositions to disease called miasms, specifically two miasms related to syphilis and gonorrhea respectively.

Alternative topical treatments for the skin lesions of AIDS-related KS include homeopathic preparations made from periwinkle, mistletoe, or phytolacca (poke root). Other alternative skin preparations include a selenium solution made from aloe gels, selenium, and tincture of silica; a mixture of aloe vera and dried kelp (seaweed); and a mixture of aloe vera, tea tree oil, and tincture of St. John's wort. Alternative treatments for KS lesions on the internal organs include a mixture of warm wine and Yunnan Paiyao powder, a Chinese patent medicine made from ginseng; castor oil packs; or a three-to seven-day grape fast repeated every 120 days.

Alternative systemic treatments for AIDS-related KS include:

- Naturopathic remedies: High doses of vitamin C, zinc, echinacea, or goldenseal to improve immune function; or preparations of astragalis, osha root, or licorice to suppress the HIV virus.
- Homeopathic remedies: These include a homeopathic preparation of **cyclosporine** and another made from a dilution of killed typhoid virus.
- Ozone therapy: There are isolated reports from Europe and the United States of AIDS-related KS going into several months of remission after treatment with ozone given via rectal insufflation.

Alternative treatments aimed at improving the quality of life for KS patients include Reiki, reflexology, meditation, and chromatherapy.

Coping with cancer treatment

Studies of treatment side effects in patients with epidemic KS are complicated by the difficulty of distinguishing between side effects caused by treatment aimed at the HIV retrovirus itself and those caused by treatment for KS. Common problems related to KS treatment include damage to the bone marrow, hair loss, and nerve damage from medications.

Other treatment-related problems include weight loss due to poor appetite, and swelling of body tissues due to fluid retention. Patients may be given nutritional counseling, medications to stimulate the appetite, and radiation treatment or diuretics to reduce the level of fluid in the tissues.

Clinical trials

By 2001, there were thirteen open and active clinical trials being conducted for treatments for KS, twelve for epidemic KS and one for unspecified KS. Some of these are comparing the relative effectiveness of doxorubicin, daunorubicin, and paclitaxel. Others are studies of other agents, including interleukin-11, interleukin-12, cidofovir, and **filgrastim**. One is a study of the effects of HAART on AIDS-related KS. The National Cancer Institute (NCI) reported that clinical trials of **thalidomide** indicated that the drug has some activity against epidemic KS. Updated information about the content of and patient participation in clinical trials can be obtained

KEY TERMS

Angiogenesis—The formation of blood vessels. Some complex proteins found in shark cartilage appear to prevent angiogenesis in tumor cells in laboratory tests.

Cryotherapy—A form of treating KS lesions that involves freezing them with liquid nitrogen.

Disseminated—Widely distributed or spread. Epidemic KS almost always develops into a disseminated form, in which the disease spreads throughout the patient's body.

Highly active antiretroviral therapy (HAART)—A form of drug-combination treatment for HIV infection introduced in 1998. Most HAART regimens are combinations of three or four drugs, usually nucleoside analogs and protease inhibitors.

Iatrogenic—Caused unintentionally by medical treatment. Immunosuppressive treatment-related KS is sometimes called iatrogenic KS.

Immunosuppressive—Any form of treatment that inhibits the body's normal immune response.

Indolent—Relatively inactive or slow-spreading. Classic KS is usually an indolent disease.

Liposomes—Artificial sacs composed of fatty substances that are used to coat or encapsulate an inner core containing another drug. Some drugs used to treat epidemic KS are given in the form of liposomes.

Opportunistic infections (OI)—Diseases caused by organisms that multiply to the point of producing symptoms only when the body's immune system is impaired.

at the web site of the National Cancer Institute: http://cancertrials.nci.nih.gov.

Prevention

The only known preventive strategy for reducing one's risk for epidemic KS is abstinence from intercourse or modification of sexual habits. Homosexual or bisexual males can reduce their risk of developing KS by avoiding passive anal intercourse. Women can reduce their risk by avoiding vaginal or anal intercourse with bisexual males.

Kidney transplant patients who are at increased risk of developing KS as a result of taking prednisone or other immunosuppressive drugs should consult their primary physician about possible changes in dosage.

Special concerns

The two special concerns most likely to arise with epidemic KS are social isolation due to the disfigurement caused by KS lesions on the patient's face, and spiritual or psychological concerns related to the tumor's connection to AIDS and homosexuality. There are many local and regional support groups for cancer patients that can help patients deal with concerns about appearance. With regard to religious/spiritual issues, most major Christian and Jewish bodies in the United States and Canada have task forces or working groups dealing with AIDS-related concerns. The National Catholic AIDS Network (NCAN) maintains an information database and web site (http://www.ncan.org) and accepts call-in referrals at (707) 874-3031.

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American Cancer Society (ACS). 1599 Clifton Road, NE, Atlanta, GA 30329. (404) 320-3333 or (800) ACS-2345. Fax: (404) 329-7530. Web site: <http://www.cancer.org>.

National Cancer Institute, Office of Cancer Communications. 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER (1-800-422-6237). TTY: (800) 332-8615. Web site: <http://www.nci.nih.gov>.

NIH National Center for Complementary and Alternative Medicine (NCCAM) Clearinghouse. P. O. Box 8218, Silver Spring, MD 20907-8218. TTY/TDY: (888) 644-6226. Fax: (301) 495-4957.

San Francisco AIDS Foundation (SFAF). 995 Market Street, #200, San Francisco, CA 94103. (415) 487-3000 or (800) 367-AIDS. Fax: (415) 487-3009. Web site: http://www.sfaf.org.

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Ketoconazole *see* **Antifungal therapy**

Ki67

Definition

Ki67 is a molecule that can be easily detected in growing cells in order to gain an understanding of the rate at which the cells within a tumor are growing.

Purpose

Detection of Ki67 is carried out on biopsies, samples of tumor tissue. The goal of this assay is to evaluate an important characteristic of the cells within the tumor, the percentage of tumor cells that are actively dividing and giving rise to more cancer cells. The number obtained through this examination is termed the S-phase, growth, or proliferative fraction. This information can play an important part in deciding the best treatment for a cancer patient.

Precautions

This test is performed on tissue or cells that have been removed during the initial surgery or diagnostic procedure used to determine the precise nature of the cancer. It usually does not require any new surgery or blood draw on the patient and, so, does not entail any additional precautions for the patient.

Description

Cancer is a group of diseases characterized by abnormal, or neoplastic, cellular growth in particular tissues. In many instances this growth is abnormal because cells are growing more rapidly than is normal. This unregulated growth is how a tumor is formed. A tumor is more or less a collection of cells that grow more rapidly than the surrounding normal tissue. Most importantly, this difference in growth rate is central to how many cancer drugs, termed cytotoxic agents, work. The ability of these drugs to eliminate cancer cells depends on their ability to kill cells that are actively proliferating, but do less damage to cells that are not actively dividing. This makes it useful to know how actively the cells in tumor are growing compared to the surrounding tissue. The measurement of Ki67 is one of the most common ways to measure the growth fraction of tumor cells. This molecule can be detected in the nucleus of only actively growing cells.

Analysis of Ki67 in tumors is accomplished by a pathologist who examines a piece of the tumor tissue using special techniques. The technique used is termed immunocytochemistry. This involves the preparation of a histologic section, a very thin piece of tumor tissue placed on a glass microscope slide. These kinds of tissue sections are used in the diagnosis of cancer. In the case of Ki67 assays, the section is incubated with antibodies that can react with the Ki67 molecule, and then treated with special reagents that cause a color to appear where antibody has bound. In this way, when the pathologist looks at the section using a microscope the fraction of growing cells, whose nuclei are stained for Ki67, can be determined for the tumor cells and compared with the normal tissue. In some instances, depending on the particular type of cancer, the pathologist might feel it more appropriate to use a different technique to assess the growth fraction for a specific tumor or leukemia.

KEY TERMS

Immunocytochemistry—Method for staining cells or tissues using antibodies so that the location of a target molecule can be determined

Nucleus—The part of the cell containing chromosomes

S phase—The part of the cell division cycle during which the genetic material, DNA, is duplicated

Preparation, Aftercare, and Risks

Because this test is performed on tissue or cells that had been removed during an initial **biopsy** or other diagnostic procedure, and because no new surgery or sample is required, no additional recommendations regarding preparation, aftercare, or risks are necessary.

Results

The proliferative or growth fraction as determined by Ki67 analysis is interpreted in view of what is normal for the tissue in which the tumor has been found or from which it originated. In the case of certain types of tissue—for example, brain—there is little cellular growth in normal tissue. In other cases, such as breast or the cells that line the colon, cellular growth is a normal part of the function of that tissue. The significance of an increased proliferative fraction is interpreted in light of the experience of the oncologist as well as the knowledge and experience of other clinicians as reported in the medical literature. The Ki67 result, often termed the "Ki67 labeling index," can be used in some cases as a prognostic indicator for some cancers. For example, for brain tumors, such as astrocytomas and glioblastomas, a high Ki67 labeling index is one factor that predicts a poor prognosis. For breast tumors, the clinician will consider the proliferative fraction in conjunction with other factors such as patient age, results of receptor assays, and

QUESTIONS TO ASK THE DOCTOR

- How far from normal is the Ki-67 labeling index of my tumor?
- To what extent is this result influencing the treatment I will receive?
- In your experience, does the proliferative fraction of my tumor predict a good response to chemotherapy?

whether or not there is evidence of spread of the disease to lymph nodes or other sites within the body. The value of Ki67 is not as firmly established for other cancers such as bladder or **pituitary tumors**.

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Warren Maltzman, Ph.D.

Kidney cancer

Definition

Kidney cancer is a disease in which the cells in certain tissues of the kidney start to grow uncontrollably and form tumors. Renal cell **carcinoma**, sometimes referred to as hypernephroma, occurs in the cells lining the kidneys (epithelial cells). It is the most common type of kidney cancer. Eighty-five percent of all kidney tumors are renal cell carcinomas. **Wilms' tumor** is a rapidly developing cancer of the kidney most often found in children under four years of age.

Description

The kidneys are a pair of organs shaped like kidney beans that lie on either side of the spine just above the waist. Inside each kidney are tiny tubes (tubules) that filter and clean the blood, taking out the waste products and making urine. The urine that is made by the kidney passes through a tube called the ureter into the bladder. Urine is held in the bladder until it is discharged from the body. Renal cell carcinoma (RCC) generally develops in the lining of the tubules that filter and clean the blood. Cancer that develops in the central portion of the kidney (where the urine is collected and drained into the ureters) is known as transitional cell carcinoma of the renal pelvis. Transitional cell cancer is similar to **bladder cancer**. Wilms' tumor is the most common type of childhood kidney cancer and is distinct from kidney cancer in adults.

Demographics

Kidney cancer accounts for approximately 2–3% of all cancers. In the United States, kidney cancer is the tenth most common cancer and the incidence has increased by 43% since 1973; the death rate has increased by 16%. According to the American Cancer Society, 35,710 Americans were diagnosed with kidney cancer in 2004, and 12,480 died from the disease. RCC accounts for 90–95% of malignant neoplasms that originate from the kidney.

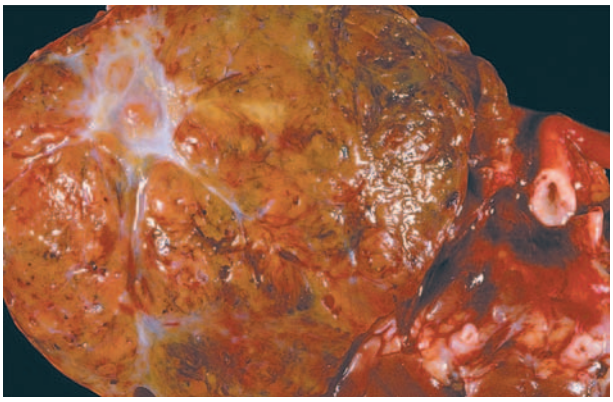
Kidney cancer occurs most often in men over the age of 40. The median age of diagnosis is 65. The male:female ratio is about 3:2.

Causes and symptoms

The causes of kidney cancer are unknown, but there are many risk factors associated with kidney cancer. The risk factors listed from greatest to smallest include:

- von Hippel-Lindau disease (>100)
- Chronic dialysis (32)
- Obesity (3.6)
- Tobacco use (2.3)
- First-degree relative with kidney cancer (1.6)
- Hypertension (1.4)
- Occupational exposure to dry cleaning solvents (1.4)
- Diuretics(non-hypertension use) (1.3)
- Trichloroethylene exposure (1.0)
- Heavy phenacetin use (1.1–6.0)
- Polycystic kidney disease (0.8–2.0)
- Cadmium exposure (1.0–3.9)
- Arsenic exposure (1.6)
- Asbestos (1.1–1.8)

The most common symptom of kidney cancer is blood in the urine (hematuria). Other symptoms include painful urination, pain in the lower back or on the sides, abdominal pain, a lump or hard mass that can be felt in the kidney area, unexplained **weight loss**, **fever**, weakness, **fatigue**, and high blood pressure.



An extracted cancerous kidney. *(Photo by Robert Riedlinger. Custom Medical Stock Photo. Reproduced by permission.)*

Diagnosis

A diagnostic examination for kidney cancer includes taking a thorough medical history and making a complete physical examination in which the doctor will probe (palpate) the abdomen for lumps. Blood tests will be ordered to check for changes in blood chemistry caused by substances released by the tumor. Laboratory tests may show abnormal levels of iron in the blood. Either a low red blood cell count (**anemia**) or a high red blood cell count (erythrocytosis) may accompany kidney cancer. Occasionally, patients will have high calcium levels.

If the doctor suspects kidney cancer, an intravenous pyelogram (also called an IVP or intravenous urography)) may be ordered. An IVP is an x-ray test in which a dye is injected into a vein in the arm. The dye travels through the body, and when it is concentrated in the urine to be discharged, it outlines the kidneys, ureters, and the urinary bladder. On an x-ray image, the dye will reveal any abnormalities of the urinary tract. The IVP may miss small kidney cancers.

Renal ultrasound is a diagnostic test in which sound waves are used to form an image of the kidneys. Ultrasound is a painless and non-invasive procedure that can be used to detect even very small kidney tumors. Imaging tests such as **computed tomography** (CT) scans and **magnetic resonance imaging** (MRI) can be used to evaluate the kidneys and the surrounding organs. These tests are used to check whether the tumor has spread outside the kidney to other organs in the abdomen. If the patient complains of **bone pain**, a special **x ray** called a bone scan may be ordered to rule out spread to the bones. A chest x ray may be taken to rule out spread to the lungs.

A kidney **biopsy** is used to positively confirm the diagnosis of kidney cancer. During this procedure, a small piece of tissue is removed from the tumor and examined under a microscope. The biopsy will give information about the type of tumor, the cells that are involved, and the aggressiveness of the tumor (tumor stage).

Staging, treatment, and prognosis

Staging

Staging guidelines for kidney cancer are as follows (2.5 cm equals approximately 1 in):

- Stage I: Primary tumor is 5 cm or less in greatest dimension and is limited to the kidney, with no lymph node involvement.
- Stage II: Primary tumor is larger than 5 cm in greatest dimension and is limited to the kidney, with no lymph node involvement.
- Stage III: Primary tumor may extend into major veins or invade adrenal glands or perinephric tissues, but not beyond Gerota's fascia. There may be **metastasis** in a single lymph node.
- Stage IV: Primary tumor invades beyond Gerota's fascia. Metastasis in more than one lymph node. Possible metastasis to distant structures in the body.

Treatment

Each person's treatment is different and depends on several factors. The location, size, and extent of the tumor have to be considered in addition to the patient's age, general health, and medical history. In addation, much has changed in the treatment and management of kidney cancer since the 1980s, including new surgical techniques, new anticancer drugs, and the development of effective treatments for advanced disease.

The primary treatment for kidney cancer that has not spread to other parts of the body, which is a Stage I, II, or III tumor, is surgical removal of the diseased kidney (nephrectomy). Because most cancers affect only one kidney, the patient can function well with the remaining one. Two types of surgical procedure are used. Radical nephrectomy removes the entire kidney and the surrounding tissue. Sometimes, the lymph nodes surrounding the kidney are also removed. Partial nephrectomy removes only part of the kidney along with the tumor. This procedure is used either when the tumor is very small or when it is not practical to remove the entire kidney. It is not practical to remove a kidney when the patient has only one kidney or when both kidneys have tumors. There is a small (5%) chance of missing some of the cancer. Nephrectomy can also be useful for Stage IV cancers, but alternative surgical procedures such as transarterial angioinfarction may be used.

The rapid development and widespread use of laparoscopic techniques has made it possible for surgeons to

remove small tumors while sparing the rest of the kidney. Most tumors removed by laparoscopy are 4 cm (1.6 in) in size or smaller. Laparoscopy also allows the surgeon to remove small tumors with cryoablation (destroying the tumor by freezing it) rather than cutting.

Radiation therapy, which consists of exposing the cancer cells to high-energy gamma rays from an external source, generally destroys cancer cells with minimal damage to the normal tissue. Side effects are nausea, fatigue, and stomach upsets. These symptoms disappear when the treatment is over. In kidney cancer, radiation therapy has been shown to alleviate pain and bleeding, especially when the cancer is inoperable. However, it has not proven to be of much use in destroying the kidney cancer cells. Therefore radiation therapy is not used very often as a treatment for cancer or as a routine adjuvant to nephrectomy. Radiotherapy, however, is used to manage metastatic kidney cancer.

Treatment of kidney cancer with anticancer drugs (**chemotherapy**) has not produced good results. However, new drugs and new combinations of drugs continue to be tested in **clinical trials**. One new drug, semaxanib (SU5416), is reported to have good results in treating patients with kidney cancer. As of 2004, however, semaxanib is still undergoing clinical trials in the United States.

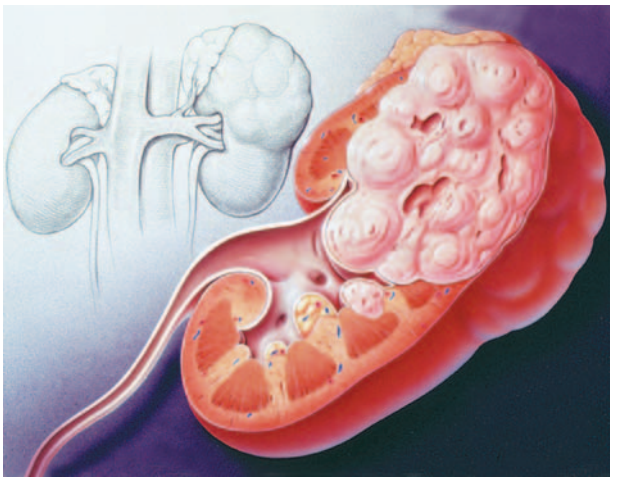
Immunologic therapy (or immunotherapy), a form of treatment in which the body's immune system is harnessed to help fight the cancer, is a new mode of therapy that is being tested for kidney cancer. Clinical trials with substances produced by the immune cells (**aldesleukin** and interferon) have shown some promise in destroying kidney cancer cells. These substances have been approved for use but they can be very toxic and produce severe side effects. The benefits derived from the treatment have to be weighed very carefully against the side effects in each case. Immunotherapy is the most promising systemic therapy for metastatic kidney cancer.

Prognosis

Because kidney cancer is often caught early and sometimes progresses slowly, the chances of a surgical cure are good. It is also one of the few cancers for which there are well-documented cases of spontaneous remission without therapy.

Alternative and complementary therapies

There are several healing philosophies, approaches, and therapies that may be used as supplemental or instead of traditional treatments. All of the items listed



Background of illustration and to left: a pair of kidneys. One kidney is normal, while the other is cancerous. The foreground of the illustration and in color: a cutaway of the cancerous kidney. *(Custom Medical Stock Photo. Reproduced by permission.)*

may have varying effectiveness in boosting the immune system and/or treating a tumor. The efficacy of each treatment also varies from person to person. None of the treatments, however, have demonstrated safety or effectiveness on a consistent basis. Patients should research such treatments for any potential dangers (laetrile, for example, has caused death due to cyanide poisoning) and notify their physician before taking them.

- 714-X
- antineoplastons
- Cancell
- cartilage (bovine and shark)
- Coenzyme Q10
- Gerson Therapy
- Gonzalez Protocol
- Hydrazine sulfate
- immuno-augementative therapy
- Laetrile
- mistletoe

Coping with cancer treatment

Side effects of treatment, as well as nutrition, emotional well-being, and other complications, are all parts of coping with cancer. There are many possible side effects for a cancer treatment that include:

- constipation
- delirium

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Bone scan—An x-ray study in which patients are given an intravenous injection of a small amount of a radioactive material that travels in the blood. When it reaches the bones, it can be detected by x ray to make a picture of their internal structure.

Chemotherapy—Treatment with anticancer drugs.

Computed tomography (CT) scan—A medical procedure in which a series of x-ray images are made and put together by a computer to form detailed pictures of areas inside the body.

Cryoablation—A technique for removing tissue by destroying it with extreme cold.

Hematuria—Blood in the urine.

Immunotherapy—Treatment of cancer by stimulating the body's immune defense system.

Intravenous pyelogram (IVP)—A procedure in which a dye is injected into a vein in the arm. The dye travels through the body and concentrates in the urine to be discharged. It outlines the kidneys, ureters, and the urinary bladder. An x-ray image is then made and any abnormalities of the urinary tract are revealed.

Magnetic resonance imaging (MRI)—A medical procedure used for diagnostic purposes in which pictures of areas inside the body can be created using a magnet linked to a computer.

Nephrectomy—A medical procedure in which the kidney is surgically removed.

Primary tumor—A cancer's origin or initial growth.

Radiation therapy—Treatment with high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Renal ultrasound—A painless and non-invasive procedure in which sound waves are bounced off the kidneys. These sound waves produce a pattern of echoes that are then used by the computer to create pictures of areas inside the kidney (sonograms).

QUESTIONS TO ASK THE DOCTOR

- What should I expect from a biopsy test?
- What type of kidney cancer do I have?
- What is the stage of the disease?
- What are the treatment choices? Which do you recommend? Why?
- What are the risks and possible side effects of each treatment?
- What are the chances that the treatment will be successful?
- What new treatments are being studied in clinical trials?
- How long will treatment last?
- Will I have to stay in the hospital?
- Will treatment affect my normal activities? If so, for how long?
- What is the treatment likely to cost?

- fatigue
- fever, chills, sweats
- nausea and vomiting
- mouth sores, dry mouth, bleeding gums
- pruritus (itching)
- **sexuality**
- sleep disorders

Anxiety, **depression**, loss, post-traumatic stress disorder, sexuality, and substance abuse are all possible emotional side-effects. Nutrition and eating before, during, and after a treatment can also be of concern. Other complications of coping with cancer include fever and pain.

Clinical trials

As of 2005, the National Cancer Institute (NCI) listed 73 clinical trials in place across the United States studying new types of radiation therapy and chemotherapy, new drugs and drug combinations, biological therapies, ways of combining various types of treatment for kidney cancer, side effect reduction, and improving quality of life. Immunostimulatory agents and gene-therapy techniques that modify tumor cells, antiangiogenesis compounds, cyclin-dependent kinase inhibitors, and differentiating agents are all being investigated as possible therapies. The reader may consult <http://ClinicalTrials.gov> and a doctor for a list of kidney cancer clinical trials.

Prevention

The exact cause of kidney cancer is not known, so it is not possible to prevent all cases. However, because a strong association between kidney cancer and tobacco has been shown, avoiding tobacco is the best way to lower one's risk of developing this cancer. Using care when working with cancer-causing agents such as asbestos and cadmium and eating a well-balanced diet may also help prevent kidney cancer.

See also Renal pelvis tumors; von Hippel-Lindau syndrome.

Resources

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American Cancer Society (National Headquarters). 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) 227-2345. <http://www.cancer.org>.

American Foundation for Urologic Disease. E-mail: admin@afud.org.

American Urological Association. 1120 N. Charles St., Baltimore, MD 21201. (410) 727-1100. <http://www.auanet.org/patient_info/find_urologist/index.cfm>.

Cancer Research Institute (National Headquarters). 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

Kidney Cancer Association. 1234 Sherman Ave., Suite 203, Evanston, IL 60202-1375. (800) 850-9132. <http://www.kidneycancerassociation.org>.

National Cancer Institute (NCI). 9000 Rockville Pike, Building 31, Room 10A16, Bethesda, MD 20892. (800) 422-6237. <http://www.nci.nih.gov>.

National Kidney Cancer Association. 1234 Sherman Ave., Suite 203, Evanston, IL 60202-1375. (800) 850-9132.

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L

Lactulose *see* **Laxatives**

Lambert-Eaton syndrome
see **Eaton-Lambert syndrome**

Lambert-Eaton Myasthenic syndrome
see **Eaton-Lambert syndrome**

Langerhans cell histiocytosis
see **Histiocytosis X**

Laparoscopy

Definition

Laparoscopy is a type of surgical procedure in which a small incision is made, usually in the navel, through which a viewing tube (laparoscope) is inserted. The viewing tube has a small camera on the eyepiece. This allows the doctor to examine the abdominal and pelvic organs on a video monitor connected to the tube. Other small incisions can be made to insert instruments to perform procedures. Laparoscopy can be done to diagnose conditions or to perform certain types of operations. It is less invasive than regular open abdominal surgery (laparotomy).

Purpose

Since the late 1980s, laparoscopy has been a popular diagnostic and treatment tool. The technique dates back to 1901, when it was reportedly first used in a gynecologic procedure performed in Russia. In fact, gynecologists were the first to use laparoscopy to diagnose and treat conditions relating to the female reproductive organs: uterus, fallopian tubes, and ovaries.

Laparoscopy was first used with cancer patients in 1973. In these first cases, the procedure was used to observe and **biopsy** the liver. Laparoscopy plays a role in the diagnosis, staging, and treatment for a variety of cancers.

As of 2001, the use of laparoscopy to completely remove cancerous growths and surrounding tissues (in place of open surgery) is controversial. The procedure is being studied to determine if it is as effective as open surgery in complex operations. Laparoscopy is also being investigated as a screening tool for **ovarian cancer**.

Laparoscopy is widely used in procedures for noncancerous conditions that in the past required open surgery, such as removal of the appendix (appendectomy) and gallbladder removal (cholecystectomy).

Diagnostic procedure

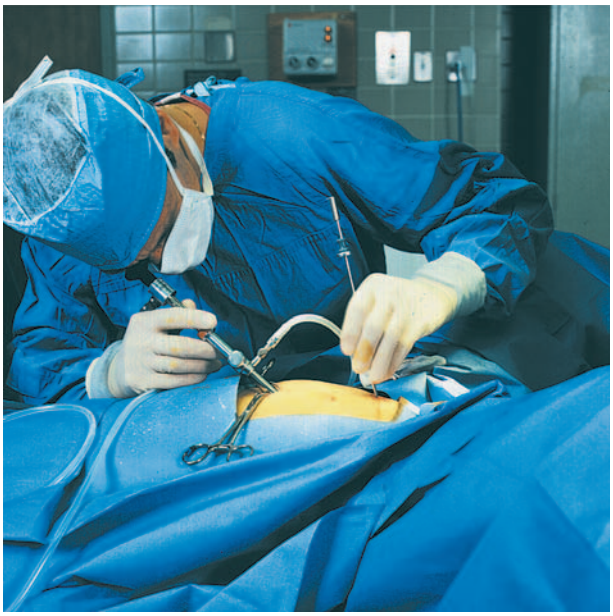
As a diagnostic procedure, laparoscopy is useful in taking biopsies of abdominal or pelvic growths, as well as lymph nodes. It allows the doctor to examine the abdominal area, including the female organs, appendix, gallbladder, stomach, and the liver.

Laparoscopy is used to determine the cause of pelvic pain or gynecological symptoms that cannot be confirmed by a physical exam or ultrasound. For example, ovarian cysts, endometriosis, ectopic pregnancy, or blocked fallopian tubes can be diagnosed using this procedure. It is an important tool when trying to determine the cause of infertility.

Operative procedure

While laparoscopic surgery to completely remove cancerous tumors, surrounding tissues, and lymph nodes is used on a limited basis, this type of operation is widely used in noncancerous conditions that once required open surgery. These conditions include:

- Tubal ligation. In this procedure, the fallopian tubes are sealed or cut to prevent subsequent pregnancies.
- Ectopic pregnancy. If a fertilized egg becomes embedded outside the uterus, usually in the fallopian tube, an operation must be performed to remove the developing embryo. This often can be done with laparoscopy.



This surgeon is performing a laparoscopic procedure on a patient. *(Photo Researchers, Inc. Reproduced by permission.)*

- Endometriosis. This is a condition in which tissue from inside the uterus is found outside the uterus in other parts of (or on organs within) the pelvic cavity. This can cause cysts to form. Endometriosis is diagnosed with laparoscopy, and in some cases the cysts and other tissue can be removed during laparoscopy.
- Hysterectomy. This procedure to remove the uterus can, in some cases, be performed using laparoscopy. The uterus is cut away with the aid of the laparoscopic instruments and then the uterus is removed through the vagina.
- Ovarian masses. Tumors or cysts in the ovaries can be removed using laparoscopy.
- Appendectomy. This surgery to remove an inflamed appendix required open surgery in the past. It is now routinely performed with laparoscopy.
- Cholecystectomy. Like appendectomy, this procedure to remove the gallbladder used to require open surgery. Now it can be performed with laparoscopy, in some cases.

In contrast to open abdominal surgery, laparoscopy usually involves less pain, less risk, less scarring, and faster recovery. Because laparoscopy is so much less invasive than traditional abdominal surgery, patients can leave the hospital sooner.

Cancer staging

Laparoscopy can be used in determining the spread of certain cancers. Sometimes it is combined with ultrasound. Although laparoscopy is a useful staging tool, its use depends on a variety of factors, which are considered for each patient. Types of cancers where laparoscopy may be used to determine the spread of the disease include:

- Liver cancer. Laparoscopy is an important tool for determining if cancer is present in the liver. When a patient has non-liver cancer, the liver is often checked to see if the cancer has spread there. Laparoscopy can identify up to 90% of malignant lesions that have spread to that organ from a cancer located elsewhere in the body. While computed tomography (CT) can find cancerous lesions that are 0.4 in (10 mm) in size, laparoscopy is capable of locating lesions that are as small as 0.04 in (1 millimeter).
- Pancreatic cancer. Laparoscopy has been used to evaluate pancreatic cancer for years. In fact, the first reported use of laparoscopy in the United States was in a case involving pancreatic cancer.
- Esophageal and stomach cancers. Laparoscopy has been found to be more effective than **magnetic resonance imaging** (MRI) or computed tomography (CT) in diagnosing the spread of cancer from these organs.
- **Hodgkin's disease**. Some patients with Hodgkin's disease have surgical procedures to evaluate lymph nodes for cancer. Laparoscopy is sometimes selected over laparotomy for this procedure. In addition, the spleen may be removed in patients with Hodgkin's disease. Laparoscopy is the standard surgical technique for this procedure, which is called a splenectomy.
- **Prostate cancer**. Patients with prostate cancer may have the nearby lymph nodes examined. Laparoscopy is an important tool in this procedure.

Cancer treatment

Laparoscopy is sometimes used as part of a palliative cancer treatment. This type of treatment is not a cure, but can often lessen the symptoms. An example is the feeding tube, which cancer patients may have if they are unable to take in food by mouth. The feeding tube provides nutrition directly into the stomach. Inserting the tube with a laparoscopy saves the patient the ordeal of open surgery.

Precautions

As with any surgery, patients should notify their physicians of any medications they are taking (prescription, over-the-counter, or herbal) and of any allergies. Precautions vary due to the several different purposes

for laparoscopy. Patients should expect to rest for several days after the procedure, and should set up a comfortable environment in their homes (with items such as pain medication, heating pads, feminine products, comfortable clothing, and food readily accessible) prior to surgery.

Description

Laparoscopy is a surgical procedure that is done in the hospital under anesthesia. For diagnosis and biopsy, local anesthesia is sometimes used. In operative procedures, such as abdominal surgery, general anesthesia is required. Before starting the procedure, a catheter is inserted through the urethra to empty the bladder, and the skin of the abdomen is cleaned.

After the patient is anesthetized, a hollow needle is inserted into the abdomen in or near the navel, and carbon dioxide gas is pumped through the needle to expand the abdomen. This allows the surgeon a better view of the internal organs. The laparoscope is then inserted through this incision to look at the internal organs. The image from the camera attached to the end of the laparoscope is seen on a video monitor.

Sometimes, additional small incisions are made to insert other instruments that are used to lift the tubes and ovaries for examination or to perform surgical procedures.

Preparation

Patients should not eat or drink after midnight on the night before the procedure.

Aftercare

After the operation, nurses will check the vital signs of patients who had general anesthesia. If there are no complications, the patient may leave the hospital within four to eight hours. (Traditional abdominal surgery requires a hospital stay of several days).

There may be some slight pain or throbbing at the incision sites in the first day or so after the procedure. The gas that is used to expand the abdomen may cause discomfort under the ribs or in the shoulder for a few days. Depending on the reason for the laparoscopy in gynecological procedures, some women may experience some vaginal bleeding. Many patients can return to work within a week of surgery and most are back to work within two weeks.

Risks

Laparoscopy is a relatively safe procedure, especially if the physician is experienced in the technique. The risk of complication is approximately 1%.

KEY TERMS

Biopsy—Microscopic evaluation of a tissue sample. The tissue is closely examined for the presence of abnormal cells.

Cancer staging—Determining the course and spread of cancer.

Cyst—An abnormal lump or swelling that is filled with fluid or other material.

Palliative treatment—A type of treatment that does not provide a cure, but eases the symptoms.

Tumor—A growth of tissue, benign or malignant, often referred to as a mass.

The procedure carries a slight risk of puncturing a blood vessel or organ, which could cause blood to seep into the abdominal cavity. Puncturing the intestines could allow intestinal contents to seep into the cavity. These are serious complications and major surgery may be required to correct the problem. For operative procedures, there is the possibility that it may become apparent that open surgery is required. Serious complications occur at a rate of only 0.2%.

Rare complications include:

- Hemorrhage
- Inflammation of the abdominal cavity lining
- Abscess
- Problems related to general anesthesia

Laparoscopy is generally not used in patients with certain heart or lung conditions, or in those who have some intestinal disorders, such as bowel obstruction.

Normal results

In diagnostic procedures, normal results would indicate no abnormalities or disease of the organs or lymph nodes that were examined.

Abnormal results

A diagnostic laparoscopy may reveal cancerous or benign masses or lesions. Abnormal findings include tumors or cysts, infections (such as pelvic inflammatory disease), cirrhosis, endometriosis, fibroid tumors, or an accumulation of fluid in the cavity. If a doctor is checking for the spread of cancer, the presence of malignant lesions in areas other than the original site of malignancy is an abnormal finding.

QUESTIONS TO ASK THE DOCTOR

- What is your complication rate?
- What is the purpose of this procedure?
- How often do you do laparoscopies?
- What type of anesthesia will be used?
- Will a biopsy be taken during the laparoscopy if anything abnormal is seen?
- If more surgery is needed, can it be done with a laparoscope?
- What area will be examined with the laparoscope?
- What are the risks?
- How long is the recovery time?

See also Endoscopic retrograde cholangiopancreatography; Gynecologic cancers; Liver biopsy; Lymph node biopsy; Nutritional support; Tumor grading; Tumor staging; Ultrasonography.

Resources

BOOKS

Kurtz, Robert C., and Robert J. Ginsberg. "Cancer Diagnosis: Endoscopy." In *Cancer: Principles & Practice of Oncology*, edited by Vincent T. DeVita, Jr. Philadelphia: Lippincott, Williams & Wilkins, 2004, 725–27.

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OTHER

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Laryngeal cancer

Definition

Laryngeal cancer is cancer of the larynx or voice box.

Description

The larynx is located where the throat divides into the esophagus and the trachea. The esophagus is the tube that takes food to the stomach. The trachea, or windpipe, takes air to the lungs. The area where the larynx is located is sometimes called the Adam's apple.

The larynx has two main functions. It contains the vocal cords, cartilage, and small muscles that make up the voice box. When a person speaks, small muscles tighten the vocal cords, narrowing the distance between them. As air is exhaled past the tightened vocal cords, it creates sounds that are formed into speech by the mouth, lips, and tongue.

The second function of the larynx is to allow air to enter the trachea and to keep food, saliva, and foreign material from entering the lungs. A flap of tissue called the epiglottis covers the trachea each time a person swallows. This blocks foreign material from entering the lungs. When not swallowing, the epiglottis retracts, and air flows into the trachea. During treatment for cancer of the larynx, both of these functions may be lost.

Cancers of the larynx develop slowly. About 95% of these cancers develop from thin, flat cells similar to skin cells called squamous epithelial cells. These cells line the larynx. Gradually, the squamous epithelial cells begin to change and are replaced with abnormal cells. These abnormal cells are not cancerous but are pre-malignant cells that have the potential to develop into cancer. This condition is called dysplasia. Most people with dysplasia never develop cancer. The condition simply goes away without any treatment, especially if the person with dysplasia stops smoking or drinking alcohol.

The larynx is made up of three parts, the glottis, the supraglottis, and the subglottis. Cancer can start in any of these regions. Treatment and survival rates depend on which parts of the larynx are affected and whether the cancer has spread to neighboring areas of the neck or distant parts of the body.

The glottis is the middle part of the larynx. It contains the vocal cords. Cancers that develop on the vocal cords are often diagnosed very early because even small vocal cord tumors cause hoarseness. In addition, the vocal cords have no connection to the lymphatic system. This means that cancers on the vocal cord do not spread easily. When confined to the vocal cords without any involvement of other parts of the larynx, the cure rate for this cancer is 75% to 95%.

The supraglottis is the area above the vocal cords. It contains the epiglottis, which protects the trachea from foreign materials. Cancers that develop in this

region are usually not found as early as cancers of the glottis because the symptoms are less distinct. The supraglottis region has many connections to the lymphatic system, so cancers in this region tend to spread easily to the lymph nodes and may spread to other parts of the body (lymph nodes are small bean-shaped structures that are found throughout the body; they produce and store infection-fighting cells). In 25% to 50% of people with cancer in the supraglottal region, the cancer has already spread to the lymph nodes by the time they are diagnosed. Because of this, survival rates are lower than for cancers that involve only the glottis.

The subglottis is the region below the vocal cords. Cancer starting in the subglottis region is rare. When it does, it is usually detected only after it has spread to the vocal cords, where it causes obvious symptoms such as hoarseness. Because the cancer has already begun to spread by the time it is detected, survival rates are generally lower than for cancers in other parts of the larynx.

Demographics

About 12,000 new cases of cancer of the larynx develop in the United States each year. Each year, about 3,900 die of the disease. Laryngeal cancer is between four and five times more common in men than in women. Almost all men who develop laryngeal cancer are over age 55. Laryngeal cancer is about 50% more common among African-American men than among other Americans.

It is thought that older men are more likely to develop laryngeal cancer than women because the two main risk factors for acquiring the disease are lifetime habits of smoking and alcohol abuse. More men smoke and drink more than women, and more African-American men are heavy smokers than other men in the United States. However, as smoking becomes more prevalent among women, it seems likely that more cases of laryngeal cancer in females will be seen.

Causes and symptoms

Laryngeal cancer develops when the normal cells lining the larynx are replaced with abnormal cells (dysplasia) that become malignant and reproduce to form tumors. The development of dysplasia is strongly linked to life-long habits of smoking and heavy use of alcohol. The more a person smokes, the greater the risk of developing laryngeal cancer. It is unusual for someone who does not smoke or drink to develop cancer of the larynx. Occasionally, however, people who inhale asbestos particles, wood dust, paint or industrial chemical fumes over a long period of time develop the disease.

The symptoms of laryngeal cancer depend on the location of the tumor. Tumors on the vocal cords are rarely painful, but cause hoarseness. Anyone who is continually hoarse for more than two weeks or who has a cough that does not go away should be checked by a doctor.

Tumors in the supraglottal region above the vocal cords often cause more, but less distinct symptoms. These include:

- persistent sore throat
- pain when swallowing
- difficulty swallowing or frequent choking on food
- bad breath
- lumps in the neck
- persistent ear pain (called referred pain; the source of the pain is not the ear)
- change in voice quality

Tumors that begin below the vocal cords are rare, but may cause noisy or difficult breathing. All the symptoms above can also be caused other cancers as well as by less serious illnesses. However, if these symptoms persist, it is important to see a doctor and find their cause, because the earlier cancer treatment begins, the more successful it is.

Diagnosis

On the first visit to a doctor for symptoms that suggest laryngeal cancer, the doctor first takes a complete medical history, including family history of cancer and lifestyle information about smoking and alcohol use. The doctor also does a physical examination, paying special attention to the neck region for lumps, tenderness, or swelling.

The next step is examination by an otolaryngologist, or ear, nose, and throat (ENT) specialist. This doctor also performs a physical examination, but in addition will also want to look inside the throat at the larynx. Initially, the doctor may spray a local anesthetic on the back of the throat to prevent gagging, then use a long-handled mirror to look at the larynx and vocal cords. This examination is done in the doctor's office. It may cause gagging but is usually painless.

A more extensive examination involves a **laryngoscopy**. In a laryngoscopy, a lighted fiberoptic tube called a laryngoscope that contains a tiny camera is inserted through the patient's nose and mouth and snaked down the throat so that the doctor can see the larynx and surrounding area. This procedure can be done with a sedative and local anesthetic in a doctor's office. More often, the procedure is done in an

outpatient surgery clinic or hospital under general anesthesia. This allows the doctor to use tiny clips on the end of the laryngoscope to take biopsies (tissue samples) of any abnormal-looking areas.

Laryngoscopies are normally painless and take about one hour. Some people find their throat feels scratchy after the procedure. Since laryngoscopies are done under sedation, patients should not drive immediately after the procedure, and should have someone available to take them home. Laryngoscopy is a standard procedure that is covered by insurance.

The locations of the samples taken during the laryngoscopy are recorded, and the samples are then sent to the laboratory where they are examined under the microscope by a pathologist who specializes in diagnosing diseases through cell samples and laboratory tests. It may take several days to get the results. Based on the findings of the pathologist, cancer can be diagnosed and staged.

Once cancer is diagnosed, other tests will probably be done to help determine the exact size and location of the tumors. This information is helpful in determining which treatments are most appropriate. These tests may include:

- Endoscopy. Similar to a laryngoscopy, this test is done when it appears that cancer may have spread to other areas, such as the esophagus or trachea.
- **Computed tomography** (CT or CAT) scan. Using x-ray images taken from several angles and computer modeling, CT scans allow parts of the body to be seen as a cross section. This helps locate and size the tumors, and provides information on whether they can be surgically removed.
- Magnetic resonance imaging (MRI). MRI uses magnets and radio waves to create more detailed cross-sectional scans than computed tomography. This detailed information is needed if surgery on the larynx area is planned.
- Barium swallow. Barium is a substance that, unlike soft tissue, shows up on x rays. Swallowed barium coats the throat and allows x-ray pictures to be made of the tissues lining the throat.
- Chest **x ray**. Done to determine if cancer has spread to the lungs. Since most people with laryngeal cancer are smokers, the risk of also having lung cancer or emphysema is high.
- Fine needle aspiration (FNA) **biopsy**. If any lumps on the neck are found, a thin needle is inserted into the lump, and some cells are removed for analysis by the pathologist.
- Additional blood and urine tests. These tests do not diagnose cancer, but help to determine the patient's general health and provide information to determine which cancer treatments are most appropriate.

Treatment team

An otolaryngologist and an oncologist (cancer specialist) generally lead the treatment team. They are supported by radiologists to interpret CT and MRI scans, a head and neck surgeon, and nurses with special training in assisting cancer patients.

A speech pathologist is often involved in treatment, both before surgery to discuss various options for communication if the larynx is removed, and after surgery to teach alternate forms of voice communication. A social worker, psychologist, or family counselor may help both the patient and the family meet the changes and challenges that living with laryngeal cancer brings.

At any point in the process, the patient may want to get a second opinion from another doctor in the same specialty. This is a common practice and does not indicate a lack of faith in the original doctor, but simply a desire for more information. Some insurance companies require a second opinion before surgery is done.

Clinical staging, treatments, and prognosis

Staging

Once cancer of the larynx is found, more tests will be done to find out if cancer cells have spread to other parts of the body. This is called staging. A doctor needs to know the stage of the disease to plan treatment. In cancer of the larynx, the definitions of the early stages depend on where the cancer started.

STAGE I. The cancer is only in the area where it started and has not spread to lymph nodes in the area or to other parts of the body. The exact definition of stage I depends on where the cancer started, as follows:

- Supraglottis: The cancer is only in one area of the supraglottis and the vocal cords can move normally.
- Glottis: The cancer is only in the vocal cords and the vocal cords can move normally.
- Subglottis: The cancer has not spread outside of the subglottis.

STAGE II. The cancer is only in the larynx and has not spread to lymph nodes in the area or to other parts of the body. The exact definition of stage II depends on where the cancer started, as follows:

- Supraglottis: The cancer is in more than one area of the supraglottis, but the vocal cords can move normally.

- Glottis: The cancer has spread to the supraglottis or the subglottis or both. The vocal cords may or may not be able to move normally.
- Subglottis: The cancer has spread to the vocal cords, which may or may not be able to move normally.

STAGE III. Either of the following may be true:

- The cancer has not spread outside of the larynx, but the vocal cords cannot move normally, or the cancer has spread to tissues next to the larynx.
- The cancer has spread to one lymph node on the same side of the neck as the cancer, and the lymph node measures no more than 3 centimeters (just over 1 inch).

STAGE IV. Any of the following may be true:

- The cancer has spread to tissues around the larynx, such as the pharynx or the tissues in the neck. The lymph nodes in the area may or may not contain cancer.
- The cancer has spread to more than one lymph node on the same side of the neck as the cancer, to lymph nodes on one or both sides of the neck, or to any lymph node that measures more than 6 centimeters (over 2 inches).
- The cancer has spread to other parts of the body.

RECURRENT Recurrent disease means that the cancer has come back (recurred) after it has been treated. It may come back in the larynx or in another part of the body.

Treatment

Treatment is based on the stage of the cancer as well as its location and the health of the individual. Generally, there are three types of treatments for cancer of the larynx. These are surgery, radiation, and **chemotherapy**. They can be used alone or in combination based in the stage of the caner. Getting a second opinion after the cancer has been staged can be very helpful in sorting out treatment options and should always be considered.

SURGERY The goal of surgery is to cut out the tissue that contains malignant cells. There are several common surgeries to treat laryngeal cancer.

Stage III and stage IV cancers are usually treated with total **laryngectomy**. This is an operation to remove the entire larynx. Sometimes other tissues around the larynx are also removed. Total laryngectomy removes the vocal cords. Alternate methods of voice communication must be learned with the help of a speech pathologist.

Smaller tumors are sometimes treated by partial laryngectomy. The goal is to remove the cancer but save as much of the larynx (and corresponding speech capability) as possible. Very small tumors or cancer in situ are sometimes successfully treated with laser excision surgery. In this type of surgery, a narrowly targeted beam of light from a laser is used to remove the cancer.

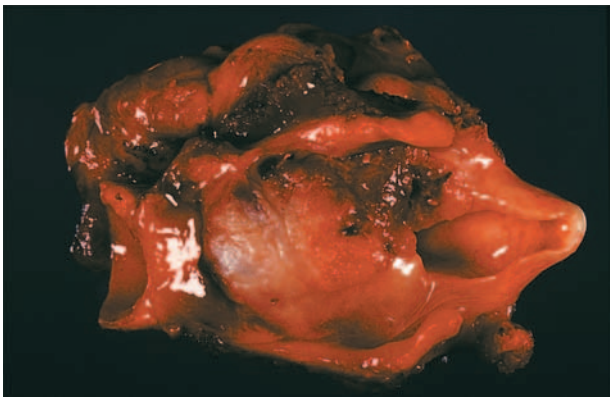
Advanced cancer (Stages III and IV) that has spread to the lymph nodes often requires an operation called a neck dissection. The goal of a neck dissection is to remove the lymph nodes and prevent the cancer from spreading. There are several forms of neck dissection. A **radical neck dissection** is the operation that removes the most tissue.

Several other operations are sometimes performed because of laryngeal cancer. A tracheotomy is a surgical procedure in which an artificial opening is made in the trachea (windpipe) to allow air into the lungs. This operation is necessary if the larynx is totally removed. A gastrectomy tube is a feeding tube placed through skin and directly into the stomach. It is used to give nutrition to people who cannot swallow or whose esophagus is blocked by a tumor. People who have a total laryngectomy usually do not need a gastrectomy tube if their esophagus remains intact.

RADIATION **Radiation therapy** uses high-energy rays, such as x rays or gamma rays, to kill cancer cells. The advantage of radiation therapy is that it preserves the larynx and the ability to speak. The disadvantage is that it may not kill all the cancer cells. Radiation therapy can be used alone in early stage cancers or in combination with surgery. Sometimes it is tried first with the plan that if it fails to cure the cancer, surgery still remains an option. Often, radiation therapy is used after surgery for advanced cancers to kill any cells the surgeon might not have removed.

There are two types of radiation therapy. External beam radiation therapy focuses rays from outside the body on the cancerous tissue. This is the most common type of radiation therapy used to treat laryngeal cancer. With internal radiation therapy, also called brachytherapy, radioactive materials are placed directly on the cancerous tissue. This type of radiation therapy is a much less common treatment for laryngeal cancer.

External radiation therapy is given in doses called fractions. A common treatment involves giving fractions five days a week for seven weeks. **Clinical trials** are underway to determine the benefits of accelerating the delivery of fractions (accelerated fractionation) or dividing fractions into smaller doses given more than once a day (hyperfractionation). Side effects of radiation therapy include dry mouth, sore throat, hoarseness, skin problems, trouble swallowing, and diminished ability to taste.



A pathology photograph of an extracted tumor found on the larynx. *(Photograph by William Gage. Custom Medical Stock Photo. Reproduced by permission.)*

CHEMOTHERAPY Chemotherapy is the use of drugs to kill cancer cells. Unlike radiation therapy, which is targeted to a specific tissue, chemotherapy drugs are either taken by mouth or intravenously (through a vein) and circulate throughout the whole body. They are used mainly to treat advanced laryngeal cancer that is inoperable or that has metastasized to a distant site. Chemotherapy is often used after surgery or in combination with radiation therapy. Clinical trials are underway to determine the best combination of treatments for advanced cancer.

The two most common chemotherapy drugs used to treat laryngeal cancer are **cisplatin** and 5-fluorouracil (5-FU or fluorouracil). There are many side effects associated with chemotherapy drugs, including **nausea and vomiting**, loss of appetite (anorexia), hair loss (alopecia), **diarrhea**, and mouth sores. Chemotherapy can also damage the blood-producing cells of the bone marrow, which can result in low blood cell counts, increased chance of infection, and abnormal bleeding or bruising.

Prognosis

Cure rates and survival rates can predict group outcomes, but can never precisely predict the outcome for a single individual. However, the earlier laryngeal cancer is discovered and treated, the more likely it will be cured.

Cancers found in stage 0 and stage 1 have a 75% to 95% cure rate depending on the site. Late stage cancers that have metastasized have a very poor survival rate, with intermediate stages falling somewhere in between. People who have had laryngeal cancer are at greatest risk for recurrence (having cancer come back), especially in the head and neck, during the first two to three years after treatment. Check-ups during the first year are needed every other month, and four times a year during the second year. It is rare for laryngeal cancer to recur after five years of being cancer-free.

Alternative and complementary therapies

Alternative and complementary therapies range from herbal remedies, vitamin supplements, and special diets to spiritual practices, acupuncture, massage, and similar treatments. When these therapies are used in addition to conventional medicine, they are called complementary therapies. When they are used instead of conventional medicine, they are called alternative therapies.

Complementary or alternative therapies are widely used by people with cancer. One large study published in the *Journal of Clinical Oncology* in July 2000, found that 83% of all cancer patients studied used some form of complementary or alternative medicine as part of their cancer treatment. No specific alternative therapies have been directed toward laryngeal cancer. However, good nutrition and activities that reduce stress and promote a positive view of life have no unwanted side effects and appear to be beneficial in boosting the immune system in fighting cancer.

Unlike traditional pharmaceuticals, complementary and alternative therapies are not evaluated by the United States Food and Drug Administration (FDA) for either safety or effectiveness. These therapies may have interactions with traditional pharmaceuticals. Patients should be wary of "miracle cures" and notify their doctors if they are using herbal remedies, vitamin supplements or other unprescribed treatments. Alternative and experimental treatments normally are not covered by insurance.

Coping with cancer treatment

Cancer treatment, even when successful, has many unwanted side effects. In laryngeal cancer, the biggest side effects are the loss of speech due to total laryngectomy and the need to breathe through a hole in the neck called a stoma. Several alternative methods of sound production, both mechanical and learned, are available, and should be discussed with a speech pathologist. Support groups also exist for people who have had their larynx removed. Coping with speech loss and care of the stoma is discussed more extensively in the laryngectomy entry.

Chemotherapy brings with it a host of unwanted side effects, many of which disappear after the chemotherapy stops. For example, hair will re-grow, and until it does, a wig can be used. Medications are available to

treat nausea and vomiting. Side effects such as dry skin are treated symptomatically.

Clinical trials

Clinical trials are government-regulated studies of new treatments and techniques that may prove beneficial in diagnosing or treating a disease. Participation is always voluntary and at no cost to the participant. Clinical trials are conducted in three phases. Phase 1 tests the safety of the treatment and looks for harmful side effects. Phase 2 tests the effectiveness of the treatment. Phase 3 compares the treatment to other treatments available for the same condition.

The selection of clinical trials underway changes frequently. Clinical trials for laryngeal cancer currently focus treating advanced cancers by combining radiation and surgical therapy, radiation and chemotherapy, and different combinations of chemotherapy drugs. Other studies are examining the most effective timing and duration of radiation therapy.

Current information on what clinical trials are available and where they are being held is available by entering the search term "laryngeal cancer" at the following web sites:

- National Cancer Institute. <http://cancer-trials.nci.nih.gov> or (800) 4-CANCER.
- National Institutes of Health Clinical Trials. <http://clinicaltrials.gov>
- Center Watch: A Clinical Trials Listing. <http://www.centerwatch.com>

Prevention

By far, the most effective way to prevent laryngeal cancer is not to smoke. Smokers who quit smoking also significantly decrease their risk of developing the disease. Other ways to prevent laryngeal cancer include limiting the use of alcohol, eating a well-balanced diet, seeking treatment for prolonged heartburn, and avoiding inhaling asbestos and chemical fumes.

Special concerns

Being diagnosed with cancer is a traumatic event. Not only is one's health affected, one's whole life suddenly revolves around trips to the doctor for cancer treatment and adjusting to the side effects of these treatments. This is stressful for both the cancer patient and his or her family members. It is not unusual for family members to feel resentful of the changes that occur in the family, and then feel guilty about feeling resentful.

KEY TERMS

Dysplasia—The abnormal change in size, shape or organization of adult cells.

Lymph—Clear, slightly yellow fluid carried by a network of thin tubes to every part of the body. Cells that fight infection are carried in the lymph.

Lymphatic system—Primary defense against infection in the body. The lymphatic system consists of tissues, organs, and channels (similar to veins) that produce, store, and transport lymph and white blood cells to fight infection.

Lymph nodes—Small, bean-shaped collections of tissue found in a lymph vessel. They produce cells and proteins that fight infection, and also filter lymph. Nodes are sometimes called lymph glands.

Malignant—Cancerous. Cells tend to reproduce without normal controls on growth and form tumors or invade other tissues.

Metastasize—Spread of cells from the original site of the cancer to other parts of the body where secondary tumors are formed.

The loss of voice because of laryngeal surgery may be the most traumatic effect of laryngeal cancer. Losing the ability to communicate easily with others can be isolating. Support groups and psychological counseling is helpful for both the cancer patient and family members. Many national organizations that support cancer education can provide information on in-person or on-line support and education groups.

See also Alcohol consumption; Cigarettes; Smoking cessation.

Resources

PERIODICALS

Ahmad, I., B. N. Kumar, K. Radford, J. O'Connell, and A. J. Batch. "Surgical Voice Restoration Following Ablative Surgery for Laryngeal and Hypopharyngeal Carcinoma." *Journal or Laryngology and Otolaryngology* 114 (July 2000): 522–5.

ORGANIZATIONS

American Cancer Society. National Headquarters, 1599 Clifton Rd. NE, Atlanta, GA 30329. 800 (ACS)-2345. <http://www.cancer.org>.

National Cancer Institute. Cancer Information Service. Bldg. 31, Room 10A19, 9000 Rockville Pike, Bethesda, MD 20892. (800) 4-CANCER. <http://www.nci.nih.gov/cancerinfo/index.html>.

QUESTIONS TO ASK THE DOCTOR

- What stage is my cancer, and what exactly does that mean?
- What are possible treatments for my cancer?
- How long will my treatment last?
- What are some of the changes in my activities that will occur because of my treatment?
- What is daily life like after a laryngectomy?
- How will I speak?
- I've heard about clinical trials using radiation and drugs to treat cancer of the larynx. Where can I find out more about these trials?
- What changes in my lifestyle can I make to help improve my chances of beating this cancer?
- How often will I have to have check-ups?
- What is the likelihood that I will survive this cancer?
- Can you suggest any support groups that would be helpful to me or my family?

National Cancer Institute Office of Cancer Complementary and Alternative Medicine. <http://occam.nci.nih.gov>.

National Center for Complementary and Alternative Medicine. P. O. Box 8218, Silver Spring, MD 20907-8281. (888) 644-6226. <http://nccam.nih.gov>.

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Tish Davidson, A.M.

Laryngeal nerve palsy

Description

Laryngeal nerve palsy is damage to the recurrent laryngeal nerve (or less commonly the vagus nerve) that results in paralysis of the larynx (voice box). Paralysis may be temporary or permanent. Damage to the recurrent laryngeal nerve is most likely to occur during surgery on the thyroid gland to treat cancer of the thyroid. Laryngeal nerve palsy is also called recurrent laryngeal nerve damage.

The vagus nerve is one of 12 cranial nerves that connect the brain to other organs in the body. It runs from the brain to the large intestine. In the neck, the vagus nerve gives off a paired branch nerve called the recurrent laryngeal nerve. The recurrent laryngeal nerves lie in grooves along either side of the trachea (windpipe) between the trachea and the thyroid gland.

The recurrent laryngeal nerve controls movement of the larynx. The larynx is located where the throat divides into the esophagus, a tube that takes food to the stomach, and the trachea (windpipe) that takes air to the lungs. The larynx contains the apparatus for voice production: the vocal cords, and the muscles and ligaments that move the vocal cords. It also controls the flow of air into the lungs. When the recurrent laryngeal nerve is damaged, the movements of the larynx are reduced. This causes voice weakness, hoarseness, or sometimes the complete loss of voice. The changes may be temporary or permanent. In rare life-threatening cases of damage, the larynx is paralyzed to the extent that air cannot enter the lungs.

Causes

Laryngeal nerve palsy is an uncommon side effect of surgery to remove the thyroid gland (thyroidectomy). It occurs in 1% to 2% of operations for total thyroidectomy to treat cancer, and less often when only part of the thyroid is removed. Damage can occur to either one or both branches of the nerve, and it can be temporary or permanent. Most people experience only transient laryngeal nerve palsy and recover their normal voice within a few weeks.

Laryngeal nerve palsy can also occur from causes unrelated to thyroid surgery. These include damage to either the vagus nerve or the laryngeal nerve, due to tumors in the neck and chest or diseases in the chest such as aortic aneurysms. Both tumors and aneurysms press on the nerve, and the pressure causes damage.

Treatments

Once the recurrent laryngeal nerve is damaged, there is no specific treatment to heal it. With time, most cases of recurrent laryngeal palsy improve on their own. In the event of severe damage, the larynx may be so paralyzed that air cannot flow past it into the lungs. When

KEY TERMS

Aortic aneurysm—The ballooning of a weak spot in the aorta (the major heart artery).

Thyroid gland—A gland that produces hormones that regulate the body's metabolism. It is shaped like a flying bat with its wings outstretched and lies over the windpipe in the front of the neck.

this happens, an emergency tracheotomy must be performed to save the patient's life. A tracheotomy is a surgical procedure to make an artificial opening in the trachea (windpipe) to allow air to bypass the larynx and enter the lungs. If paralysis of the larynx is temporary, the tracheotomy hole can be surgically closed when it is no longer needed.

Some normal variation in the location of the recurrent laryngeal nerve occurs among individuals. Occasionally the nerves are not located exactly where the surgeon expects to find them. Choosing a board certified head and neck surgeon who has had a lot of experience with thyroid operations is the best way to prevent laryngeal nerve palsy.

Alternative and complementary therapies

There are no alternative or complementary therapies to heal laryngeal nerve palsy. The passage of time alone restores speech to most people. Some alternatives for artificial speech exist for people whose loss of speech is permanent.

See also Laryngectomy.

Resources

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Tish Davidson, A.M.

Laryngectomy

Definition

Laryngectomy is the partial or complete surgical removal of the larynx, usually as a treatment for cancer of the larynx.

Purpose

Normally a laryngectomy is performed to remove tumors or cancerous tissue. In rare cases, it may be done when the larynx is badly damaged by gunshot, automobile injuries, or similar violent accidents. Laryngectomies can be total or partial. Total laryngectomies are done when cancer is advanced. The entire larynx is removed. Often if the cancer has spread, other surrounding structures in the neck, such as lymph nodes, are removed at the same time. Partial laryngectomies are done when cancer is limited to one spot. Only the area with the tumor is removed. Laryngectomies may also be performed when other cancer treatment options, such as radiation therapy or **chemotherapy**, fail.

Precautions

Laryngectomy is done only after cancer of the larynx has been diagnosed by a series of tests that allow the otolaryngologist (a specialist often called an ear, nose, and throat doctor) to look into the throat and take tissue samples (biopsies) to confirm and stage the cancer. People need to be in good general health to undergo a laryngectomy, and will have standard pre-operative blood work and tests to make sure they are able to safely withstand the operation.

Description

The larynx is located slightly below the point where the throat divides into the esophagus, which takes food to the stomach, and the trachea (windpipe), which takes air to the lungs. Because of its location, the larynx plays a critical role in normal breathing, swallowing, and speaking. Within the larynx, vocal folds (often called vocal cords) vibrate as air is exhaled past, thus creating speech. The epiglottis protects the trachea, making sure that only air gets into the lungs. When the larynx is removed, these functions are lost.

Once the larynx is removed, air can no longer flow into the lungs. During this operation, the surgeon removes the larynx through an incision in the neck. The surgeon also performs a tracheotomy. He makes an artificial opening called a stoma in the front of the neck. The upper portion of the trachea is brought to the stoma and secured, making a permanent alternate way for air to get

to the lungs. The connection between the throat and the esophagus is not normally affected, so after healing, the person whose larynx has been removed (called a laryngectomee) can eat normally. However, normal speech is no longer possible. Several alternate means of vocal communication can be learned with the help of a speech pathologist.

Preparation

As with any surgical procedure, the patient will be required to sign a consent form after the procedure is thoroughly explained. Many patients prefer a second opinion, and some insurers require it. Blood and urine studies, along with chest **x ray** and EKG may be ordered as the doctor deems necessary. The patient also has a pre-operative meeting with an anesthesiologist. If a complete laryngectomy is planned, it may be helpful to meet with a speech pathologist and/or an established laryngectomee for discussion of post-operative expectations and support.

Aftercare

A person undergoing a laryngectomy spends several days in intensive care (ICU) and receives intravenous (IV) fluids and medication. As with any major surgery, the blood pressure, pulse, and respirations are monitored regularly. The patient is encouraged to turn, cough, and deep breathe to help mobilize secretions in the lungs. One or more drains are usually inserted in the neck to remove any fluids that collect. These drains are removed after several days.

It takes two to three weeks for the tissues of the throat to heal. During this time, the laryngectomee cannot swallow food and must receive nutrition through a tube inserted through the nose and down the throat into the stomach. During this time, even people with partial laryngectomies are unable to speak.

When air is drawn in normally through the nose, it is warmed and moistened before it reaches the lungs. When air is drawn in through the stoma, it does not have the opportunity to be warmed and humidified. In order to keep the stoma from drying out and becoming crusty, laryngectomees are encouraged to breathe artificially humidified air. The stoma is usually covered with a light cloth to keep it clean and to keep unwanted particles from accidentally entering the lungs. Care of the stoma is extremely important, since it is the person's only way to get air to the lungs. After a laryngectomy, a healthcare professional will teach the laryngectomee and his or her caregivers how to care for the stoma.

Immediately after a laryngectomy, an alternate method of communication such as writing notes, gesturing, or pointing must be used. A partial laryngectomy patient will gradually regain some speech several weeks after the operation, but the voice may be hoarse, weak, and strained. A speech pathologist will work with a complete laryngectomee to establish new ways of communicating.

KEY TERMS

Larynx—Also known as the voice box, the larynx is composed of cartilage that contains the apparatus for voice production. This includes the vocal cords and the muscles and ligaments that move the cords.

Lymph nodes—Accumulations of tissue along a lymph channel, which produce cells called lymphocytes that fight infection.

Tracheostomy—A surgical procedure in which an artificial opening is made in the trachea (windpipe) to allow air into the lungs.

There are three main methods of vocalizing after a total laryngectomy. In esophageal speech the laryngectomee learns how to "swallow" air down into the esophagus and creates sounds by releasing the air. This method requires quite a bit of coordination and learning, and produces short bursts (7 or 8 syllables) of low-volume sound.

Tracheoesophageal speech diverts air through a hole in the trachea made by the surgeon. The air then passes through an implanted artificial voice prosthesis (a small tube that makes a sound when air goes through it). Recent advances have been made in implanting voice prostheses that produce good voice quality.

The third method of artificial sound communication involves using a hand-held electronic device that translates vibrations into sounds. There are several different styles of these devices, but all require the use of at least one hand to hold the device to the throat. The choice of which method to use depends on many things including the age and health of the laryngectomee, and whether other parts of the mouth, such as the tongue, have also been removed.

Many patients resume daily activities after surgery. Special precautions must be taken during showering or shaving. Special instruction and equipment is also required for those who wish to swim or water ski, as it is dangerous for water to enter the windpipe and lungs through the stoma.

Regular follow-up visits are important following treatment for cancer of the larynx because there is a higher-than-average risk of developing a new cancer in the mouth, throat, or other regions of the head or neck. Many self-help and support groups are available to help patients meet others who face similar problems.

QUESTIONS TO ASK THE DOCTOR

- Is laryngectomy my only viable treatment option?
- What specific lifestyle changes will I have to make?
- Is there a support group in the area that can assist me post-surgery?
- How long will it be until I can verbally communicate? What are my options?
- How sizable is the risk of recurring cancer?

Risks

Laryngectomy is often successful in curing early stage cancers. However it does cause lifestyle changes. Laryngectomees must learn new ways of speaking. They must be continually concerned about the care of their stoma. Serious infections can occur if water or other foreign material enters the lungs through an unprotected stoma. Also, women who undergo partial laryngectomy or who learn some types of artificial speech will have a deep voice similar to that of a man. For some women this presents psychological challenges.

Normal results

Ideally, removal of the larynx will remove all cancerous material. The person will recover from the operation, make lifestyle adjustments, and return to an active life.

Abnormal results

Sometimes cancer has spread to surrounding tissues and it is necessary to remove lymph nodes, parts of the tongue, or other cancerous tissues. As with any major operation, post-surgical infection is possible. Infection is of particular concern to laryngectomees who have chosen to have a voice prosthesis implanted, and is one of the major reasons for having to remove the device.

Resources

ORGANIZATIONS

American Cancer Society. National Headquarters, 1599 Clifton Road NE, Atlanta, GA 30329. (800) ACS -2345.<http://www.cancer.org>.

Cancer Information Service. National Cancer Institute, Building 31, Room 10A19, 9000 Rockville Pike, Bethesda, MD 20892. (800)4-CANCER. <http://www.nci.nih.gov/cancerinfo/index.html>.

International Association of Laryngectomees(IAL). <http://www.larynxlink.com/>.

National Institute on Deafness and Other Communication Disorders. National Institutes of Health, 31 Center Drive, MSC 2320, Bethesda, MD 20892-2320. <http://www.nidcd.nih.gov>.

The Voice Center at Eastern Virginia Medical School. Norfolk, VA 23507 <http://www.voice-center.com>.

Kathleen Dredge Wright
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Laryngoscopy

Definition

Laryngoscopy refers to a procedure used to view the inside of the larynx (the voice box).

Description

The purpose and advantage of seeing inside the larynx is to detect tumors, foreign bodies, nerve or structural injury, or other abnormalities. Two methods allow the larynx to be seen directly during the examination. In one, a flexible tube with a fiber-optic device is threaded through the nasal passage and down into the throat. The other method uses a rigid viewing tube passed directly from the mouth, through the throat, into the larynx. A light and lens affixed to the endoscope are used in both methods. The endoscopic tube may also be equipped to suction debris or remove material for **biopsy**. **Bronchoscopy** is a similar, but more extensive procedure in which the tube is continued through the larynx, down into the trachea and bronchi.

Preparation

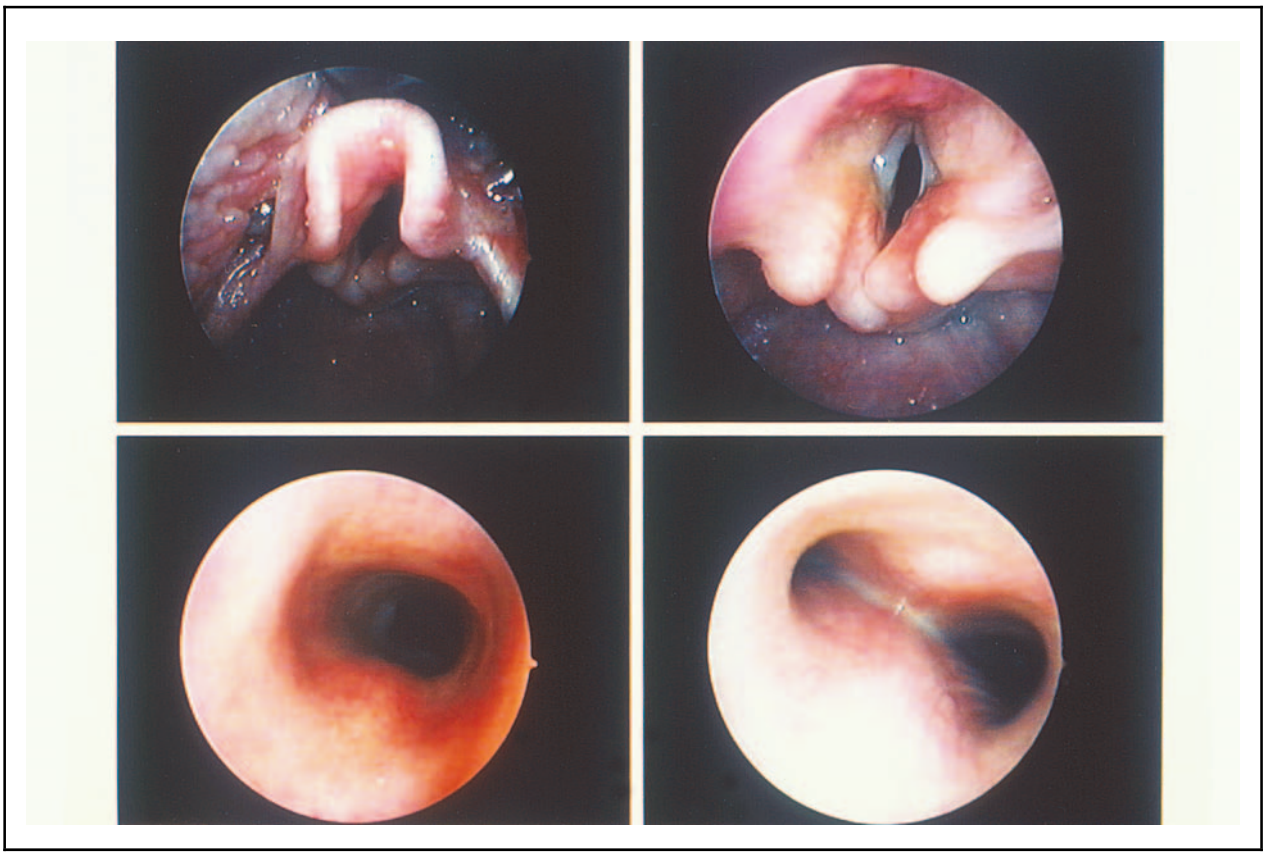
Laryngoscopy is done in the hospital with a local anesthetic spray to minimize discomfort and suppress the gag reflex. Patients are requested not to eat for several hours before the examination.

Aftercare

If the throat is sore, soothing liquids or lozenges will probably relieve any temporary discomfort.

Risks

This procedure carries no serious risks, although the patient may experience soreness of the throat or



Laryngoscopy. Multiple images of epiglottis, vocal cords, and interior of trachea and bronchus. *(Custom Medical Stock Photo. Reproduced by permission.)*

KEY TERMS

Endoscopic tube—A tube that is inserted into a hollow organ permitting a physician to see the inside it.

cough up small amounts of blood until the irritation subsides.

Normal results

A normal result would be the absence of signs of disease or damage.

Abnormal results

An abnormal finding, such as a tumor or an object lodged in the tissue, would either be removed or described for further medical attention.

Jill S. Lasker

Laxatives

Definition

A laxative is a drug that promotes bowel movements.

Purpose

Laxatives are used to prevent or treat constipation. They are also used to prepare the bowel for an examination or surgical procedure.

Description

Laxatives work in different ways, by stimulating colon movement, adding bulk to the contents of the colon, or drawing fluid or fat into the intestine. Some laxatives work by combining these functions. Most primary care physicians recommend that patients try the bulk-producing laxatives first before taking saline or stimulant laxatives.

Bisacodyl

Bisacodyl is a non-prescription stimulant laxative. It reduces short-term constipation and is also used to prepare the colon or rectum for an examination or surgical procedure. The drug works by stimulating colon movement (peristalsis); constipation is usually relieved within 15 minutes to one hour after administration of a suppository form and in 6 to 12 hours after taking the drug orally.

Calcium polycarbophil

Calcium polycarbophil is a non-prescription bulk-forming laxative that is used to reduce both constipation and **diarrhea**. It draws water to the intestine, enlarging the size of the colon and thereby stimulating movement. It reduces diarrhea by taking extra water away from the stool. This drug should relieve constipation in 12 to 24 hours and have maximum effect in three days. Colitis patients should see a reduction in diarrhea within one week.

Docusate calcium/docusate sodium

Docusate, a non-prescription laxative, helps a patient avoid constipation by softening the stool. It works by increasing the penetration of fluids into the stool by emulsifying feces, water and fat. Docusate prevents constipation and softens bowel movements and fecal impactions. This laxative should relieve constipation within one to three days.

Lactulose

Lactulose, a prescription laxative, reduces constipation and lowers blood ammonia levels. It works by drawing fluid into the intestine, raising the amount of water in the stool, and preventing the colon from absorbing ammonia. It is used to help people who suffer from chronic constipation.

Psyllium

Psyllium is a non-prescription bulk-forming laxative that reduces both constipation and diarrhea. It mixes with water to form a gel-like mass that can be easily passed through the colon. Constipation is relieved in 12 to 24 hours and maximum relief is achieved after several days.

Senna/senokot

Senna/senokot is a non-prescription laxative that reduces constipation by promoting colon movement. It is used to treat bouts of constipation and to prepare the colon for an examination or surgical procedure. This laxative reduces constipation in eight to 10 hours.

New and investigational treatments for constipation

Some newer options for the treatment of chronic constipation are being developed by various groups of researchers. These include such alternative therapies as biofeedback; newer drugs like tegaserod (Zelnorm) and prucalopride, which stimulate peristalsis; a nerve growth factor known as neurotrophin-3; and electrical stimulation of the colon.

Recommended dosage

Laxatives may be taken by mouth or rectally (suppository or enema).

Bisacodyl

- Adults or children over 12 years: 5 to 15 mg taken by mouth in morning or afternoon (up to 30 mg for surgical or exam preparation).
- Adult (rectal): 10 mg.
- Children age 2 to 11 years: 10 mg rectally as single dose.
- Children over three years: 5 to 10 mg by mouth as single dose.
- Children under two years: 5 mg rectally as single dose.

Calcium polycarbophil

- Adult: 1 g by mouth every day, up to four times a day as needed (not to exceed 6 g by mouth in a 24-hour time period).
- Children age 6 to 12 years: 500 mg by mouth twice a day as needed (not to exceed 3 g in a 24-hour time period).
- Children age 3 to 6 years: 500 mg twice a day by mouth, as needed (not to exceed 1.5 g in a 24-hour time period).

Docusate

- Adult (docusate sodium): 50 to 300 mg by mouth per day.
- Adult (docusate calcium or docusate potassium): 240 mg by mouth as needed.
- Adult (docusate sodium enema): 5 ml.
- Children over 12 years (docusate sodium enema): 2 ml.
- Children age 6 to 12 years (docusate sodium): 40 to 120 mg by mouth per day.
- Children age 3 to 6 years (docusate sodium): 20 to 60 mg by mouth per day.

- Children under 3 years (docusate sodium): 10 to 40 mg by mouth every day.

Lactulose

FOR CONSTIPATION:

- Adult: 15 to 60 ml by mouth every day.
- Children: 7.5 ml by mouth every day.

FOR ENCEPHALOPATHY:

- Adult: 20 to 30 g three or four times a day until stools become soft. Retention enema: 30 to 45 ml in 100 ml of fluid.
- Infants and children: Parents should follow physician's directions for infants and children with encephalopathy.

Psyllium

- Adult: 1 to 2 teaspoons mixed in 8 ounces of water two or three times a day by mouth, followed by 8 ounces water; or one packet in 8 ounces water two or three times a day, followed by 8 ounces of water.
- Children over 6 years: 1 teaspoon mixed in 4 ounces of water at bedtime.

Senna/senokot

- Adult (Senokot): 1 to 8 tablets taken by mouth per day or 1/2 to 4 teaspoons of granules mixed in water or juice.
- Adult (rectal suppository): 1 to 2 at bedtime.
- Adult (syrup): 1 to 4 teaspoons at bedtime.
- Adult (Black Draught): 3/4 ounce dissolved in 2.5 ounces liquid given between 2 p.m. and 4 p.m. on the day prior to a medical exam or procedure.
- Children: Parents should ask their doctor as dosage is based on weight. Black Draught is not to be used by children.
- Children age 1 month to 1 year (Senokot): 1.25 to 2.5 ml of syrup at bedtime.

Precautions

The doctor should be informed of any prior allergic drug reaction, especially prior reactions to any laxatives. Pregnancy is also a concern. Animal studies have shown laxatives to have adverse effects on pregnancy, but no human studies regarding pregnancy are currently available. These drugs are only given in pregnancy after the risks to the fetus have been taken under consideration. Nursing mothers should use caution and consult their doctors before receiving these drugs.

Bisacodyl should not be administered to patients with rectal fissures, abdominal pain, nausea, vomiting, appendicitis, abdominal surgery, ulcerated hemorrhoids, acute hepatitis, fecal impaction, or blockage in the biliary tract. Calcium polycarbophil should not be given to anyone with a gastrointestinal blockage (obstruction).

Both psyllium and docusate calcium/docusate sodium should be avoided by patients with intestinal blockage, fecal impaction, or **nausea and vomiting**. Lactulose should be avoided by patients who are elderly, have diabetes mellitus, eat a low galactose diet, or whose general health is poor.

Senna/senokot is inadvisable for patients with congestive heart failure, gastrointestinal bleeding, intestinal blockage, abdominal pain, nausea and vomiting, appendicitis, or prior abdominal surgery.

The American College of Toxicology states that cathartics should *not* be used as a means of clearing poisons from the digestive tract of a poisoning victim. Although some physicians have administered these laxatives along with activated charcoal in order to reduce the body's absorption of the poison, this treatment is no longer recommended.

Side effects

Laxatives may have side effects. Some, such as nausea and vomiting, are more common than others. Side effects related to specific laxatives are described in this section. With repeated use, people may become dependent on laxatives. All side effects should be reported to a doctor.

Bisacodyl

Common side effects:

- nausea
- vomiting
- loss of appetite (anorexia)
- cramps

Less common side effects:

- muscle weakness
- diarrhea
- electrolyte changes
- rectal burning (when suppositories are used).

Life-threatening:

- severe muscle spasms (tetany)

Calcium polycarbophil

Side effects may include:

- abdominal bloating (distention)
- gas
- laxative dependency

Life-threatening:

- gastrointestinal obstruction

Docusate calcium/docusate sodium

Side effects include:

- bitter taste in the mouth
- irritated throat
- nausea
- cramps
- diarrhea
- loss of appetite
- rash

Lactulose

Common side effects include:

- nausea
- vomiting
- loss of appetite
- abdominal cramping
- bloating
- belching
- diarrhea

Psyllium

Common side effects include:

- nausea
- vomiting
- loss of appetite
- diarrhea

Less common side effects include:

- abdominal cramping
- blockage of the esophagus or intestine

KEY TERMS

Cathartic—A general term for any agent that causes the bowel to empty. Cathartics are also known as purgatives.

Constipation—Difficult or infrequent bowel movements.

Diarrhea—Frequent, watery stools.

Electrolyte levels—In the bloodstream, electrolyte levels are the amounts of certain acids, bases, and salts. Abnormal levels of certain electrolyes can be life-threatening.

Encephalopathy—a brain disease

Peristalsis—Wave-like movement of the colon to pass feces along.

Tetany—Muscle spasms that can be life-threatening.

Senna/senokot

Common side effects include:

- nausea
- vomiting
- loss of appetite
- abdominal cramping

Less common side effects include:

- diarrhea
- gas
- urine that is pink-red or brown-black in color
- abnormal electrolyte levels

Life-threatening:

- Severe muscle spasms (tetany)

Interactions

Laxatives may interact with other drugs. Sometimes, the laxative can interfere with proper absorption of another drug. A patient must notify their doctor or pharmacist if he or she is already taking any medications so that the proper laxative can be selected or prescribed. Specific drug interactions are:

- Bisacodyl: Antacids, H2-blockers, and some herbal remedies (lily of the valley, pheasant's eye, squill).
- Calcium polycarbophil: (lowers the absorption of) tetracycline.

- Docusate calcium/docusate sodium: Unknown.
- Lactulose: Neomycin and other laxatives.
- Psyllium: Cardiac glycosides, oral anticoagulants, and salicylates.
- Senna/senokot: Disulfiram should never be taken with this drug. Also, senna/senokot lowers the absorption of other drugs taken by mouth.

Resources

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Schiller, L. R. "New and Emerging Treatment Options for Chronic Constipation." *Reviews in Gastroenterological Disorders* 4, Supplement 2 (2004): S43–S51.

Talley, N. J. "Management of Chronic Constipation." *Reviews in Gastroenterological Disorders* 4 (Winter 2004): 18–24.

ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657–3000. <www.ashp.org>.

National Digestive Diseases Information Clearinghouse. 2 Information Way, Bethesda, MD 20892-3570. nddic@aerie.com. <http://www.niddk.nih.gov/Brochures/NDDIC.htm>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

Rhonda Cloos, R.N.
Rebecca J. Frey, Ph.D.

Leiomyosarcoma

Definition

Leiomyosarcoma is cancer that consists of smooth muscle cells and small cell sarcoma tumor. The cancer begins in smooth muscle cells that grow uncontrollably and form tumors.

Description

Leiomyosarcomas can start in any organ that contains smooth muscle, but can be found in the walls of the stomach, large and small intestines, esophagus, uterus, or deep within the abdomen (retroperitoneal). But for perspective, smooth muscle cancers are quite rare: Less than 1% of all cancers are leiomyosarcomas. Very rarely, leiomyosarcomas begin in blood vessels or in the skin.

Most leiomyosarcomas are in the stomach. The second most common site is the small bowel, followed by the colon, rectum, and esophagus.

Demographics

Leiomyosarcomas do occur in the breast and uterus, but they are very rare. Uterine **sarcomas** comprise less than 1% of gynecological malignancies and 2% to 5% of all uterine malignancies. Of these numbers, leiomyosarcomas are found in only 0.1% of women of childbearing age who have tumors of the uterus. Less than 2% of tumors in women over age 60 who are undergoing hysterectomy are leiomyosarcomas.

Causes and symptoms

The exact causes of leiomyosarcoma are not known, but there are genetic and environmental risk factors associated with it. Certain inherited conditions that run in families may increase the risk of developing leiomyosarcoma. High-dose radiation exposure, such as radiotherapy used to treat other types of cancer, has also been linked to leiomyosarcoma. It is possible that exposure to certain chemical herbicides may increase the risk of developing sarcomas, but this association has not been proven.

Since leiomyosarcoma can occur in any location, the symptoms are different and depend on the site of the tumor. When leiomyosarcoma begins in an organ in the abdomen, such as the stomach or small bowel, the physician may be able to feel a large lump or mass when he examines the abdomen. When leiomyosarcoma affects a blood vessel, it may block the flow of blood to the body part supplied by the artery. Commonly occurring symptoms include:

- painless lump or mass
- painful swelling
- abdominal pain
- **weight loss**
- nausea and vomiting

Diagnosis

Some patients who have leiomyosarcomas may be visiting the doctor because they have discovered a lump or mass or swelling on a body part. Others have symptoms related to the internal organ that is affected by the leiomyosarcoma. For example, a tumor in the stomach may cause nausea, feelings of fullness, internal bleeding, and weight loss. The patient's doctor will take a detailed medical history to find out about the symptoms. The history is followed by a complete physical examination with special attention to the suspicious symptom or body part.

Depending on the location of the tumor, the doctor may order **imaging studies** such as **x ray**, **computed tomography** (CT) scan, and **magnetic resonance imaging** (MRI) to help determine the size, shape, and exact location of the tumor. A **biopsy** of the tumor is necessary to make the definitive diagnosis of leiomyosarcoma. The tissue sample is examined by a pathologist (specialist in the study of diseased tissue).

Types of biopsy

The type of biopsy done depends on the location of the tumor. For some small tumors, the doctor may perform an excisional biopsy, removing the entire tumor and a margin of surrounding normal tissue. Most often, the doctor will perform an incisional biopsy, a procedure that involves cutting out only a piece of the tumor that is used to determine its type and grade.

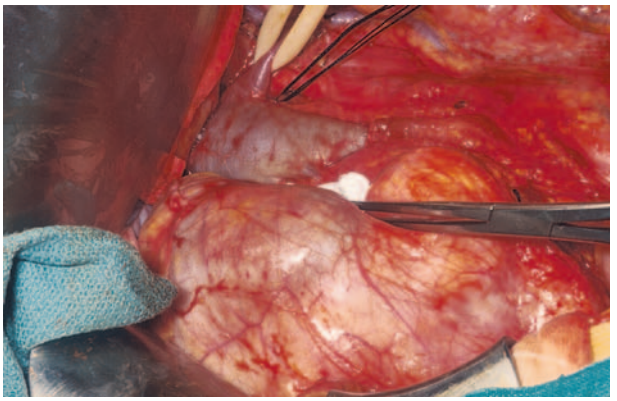
Treatment team

Patients with leiomyosarcoma are usually cared for by a multidisciplinary team of health professionals. The patient's family or primary care doctor may refer the patient to other specialists, such as surgeons and oncologists (specialists in cancer medicine), radiologic technicians, nurses, and laboratory technicians. Depending on the tumor location and treatment plan, patients may benefit from rehabilitation therapy with physical therapists and nutritional counseling from dieticians.

Clinical staging, treatments, and prognosis

Staging

The purpose of staging a tumor is to determine how far it has advanced. This is important because treatment varies depending on the stage. Stage is determined by the size of the tumor, whether the tumor has spread to nearby lymph nodes, whether the tumor has spread elsewhere in the body, and what the cells look like under the microscope.



Surgery to remove a leiomyosarcoma in the tissue near a kidney. *(Custom Medical Stock Photo. Reproduced by permission.)*

Examining the tissue sample under the microscope, using special chemical stains, the pathologist is able to classify tumors as high grade or low grade. High-grade tumors have the more rapidly growing cells and so are considered more serious.

Tumors are staged using numbers I through IV. The higher the number, the more the tumor has advanced. Stage IV leiomyosarcomas have involved either lymph nodes or have spread to distant parts of the body.

Treatment

Treatment for leiomyosarcoma varies depending on the location of the tumor, its size and grade, and the extent of its spread. Treatment planning also takes into account the patient's age, medical history, and general health.

Leiomyosarcomas on the arms and legs may be treated by **amputation** (removal of the affected limb) or by limb-sparing surgery to remove the tumor. These tumors may also be treated with **radiation therapy**, **chemotherapy**, or a combination of both.

Generally, tumors inside the abdomen are surgically removed. The site, size, and extent of the tumor determine the type of surgery performed. Leiomyosarcomas of organs in the abdomen may also be treated with radiation and chemotherapy.

Side effects

The surgical treatment of leiomyosarcoma carries risks related to the surgical site, such as loss of function

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of cancerous cells or by killing them.

Oncologist—A doctor who specializes in cancer medicine.

Pathologist—A doctor who specializes in the diagnosis of disease by studying cells and tissues under a microscope.

Radiation therapy—Treatment using high energy radiation from x-ray machines, cobalt, radium, or other sources.

Stage—A term used to describe the size and extent of spread of cancer.

resulting from amputation or from nerve and/or muscle loss. There also are risks associated with any surgical procedure, such as reactions to general anesthesia or infection after surgery.

The side effects of radiation therapy depend on the site being radiated. Radiation therapy can produce side effects such as **fatigue**, skin rashes, nausea, and **diarrhea**. Most of the side effects lessen or disappear completely after the radiation therapy has been completed.

The side effects of chemotherapy vary depending on the medication, or combination of anticancer drugs, used. Nausea, vomiting, **anemia**, lower resistance to infection, and hair loss (alopecia) are common side effects. Medication may be given to reduce the unpleasant side effects of chemotherapy.

Alternative and complementary therapies

Many patients explore alternative and complementary therapies to help to reduce the stress associated with illness, improve immune function, and feel better. While there is no evidence that these therapies specifically combat disease, activities such as biofeedback, relaxation, therapeutic touch, massage therapy, and guided imagery have been reported to enhance well-being.

Prognosis

The outlook for patients with leiomyosarcoma varies. It depends on the location and size of the tumor and its type and extent of spread. Some patients, such as those who have had small tumors located in or near the skin surgically removed, have excellent prognoses. Their 5-year survival is greater than 90%. Among patients with leiomyosarcomas in organs in the abdomen, survival is best when the tumor has been completely removed. In general, high-grade tumors that have spread widely throughout the body are not associated with favorable survival rates.

Coping with cancer treatment

Fatigue is one of the most common complaints during cancer treatment and recovery. Many patients benefit from learning energy-conserving approaches to accomplish their daily activities. They should be encouraged to rest when tired and take breaks from strenuous activities. Planning activities around times of day when energy is highest is often helpful. Mild exercise, small, frequent nutritious snacks, and limiting physical and emotional stress also help to combat fatigue.

Depression, emotional distress, and anxiety associated with the disease and its treatment may respond to counseling from a mental health professional. Many cancer patients and their families find participation in mutual aid and group support programs helps to relieve feelings of isolation and loneliness. By sharing problems with others who have lived through similar difficulties, patients and families can exchange ideas and coping strategies.

Clinical trials

Several clinical studies were underway as of 2001. For example, doctors at Memorial Sloan-Kettering Cancer Center were using specific chemotherapeutic drugs to treat patients with leiomyosarcoma that cannot be removed by surgery or has recurred. These drugs, **gemcitabine**, **docetaxel**, and **filgrastim** (G-CSF), work by stopping tumor cells from dividing, so they cannot grow. To learn more about this clinical trial and the availability of others, patients and families may wish to contact Memorial Sloan-Kettering Cancer Center at (212) 639-6555, or visit the National Cancer Institute (NCI) website at <http://cancertrials.nci.nih.gov>.

Prevention

Since the causes of leiomyosarcoma are not known, there are no recommendations about how to prevent its development. It is linked to radiation exposure; however, much of this excess radiation exposure is the result of therapy to treat other forms of cancer. Among families

QUESTIONS TO ASK THE DOCTOR

- What stage is the leiomyosarcoma?
- What are the recommended treatments?
- What are the side effects of the recommended treatment?
- Is treatment expected to cure the disease or only to prolong life?

with an inherited tendency to develop soft tissue sarcomas, careful monitoring may help to ensure early diagnosis and treatment of the disease.

Special concerns

Leiomyosarcoma, like other cancer diagnoses, may produce a range of emotional responses. Education, counseling, and participation in support group programs may help to reduce feelings of fear, anxiety and hopelessness. For many patients suffering from spiritual distress, visits with clergy members and participation in organized prayer may offer comfort.

Resources

BOOKS

Pelletier, Kenneth R. *The Best of Alternative Medicine*. New York: Simon & Schuster, 2000.

PERIODICALS

Ishida, J., et al. "Primary Leiomyosarcoma of the Greater Omentum." *Journal Of Clinical Gastroenterology* 28, no. 2 (March 1999): 167–170.

ORGANIZATIONS

American Cancer Society. 1599 Clifton Road, N.E., Atlanta, GA 30329. (800) 227–2345.

Cancer Research Institute. 681 Fifth Avenue, New York, NY 10022. (800) 992–2623.

National Cancer Institute (National Institutes of Health). 9000 Rockville Pike, Bethesda, MD 20892. (800) 422–6237.

OTHER

National Cancer Institute Clinical Cancer Trials. <http://cancertrials.nci.nih.gov>.

Barbara Wexler, M.P.H.

Letrozole *see* **Aromatase inhibitors**

Leucovorin

Definition

Leucovorin (also known as Wellcovorin and citrovorum factor or folinic acid) is a drug that can be used either to protect healthy cells from **chemotherapy** or to enhance the anti-cancer effect of chemotherapy.

Purpose

Leucovorin is most often used in cancer patients undergoing either **methotrexate** or **fluorouracil** chemotherapy. Methotrexate is used to treat a wide range of cancers including **breast cancer**, **head and neck cancers**, acute leukemias, and **Burkitt's lymphoma**. Fluorouracil is used in combination with leucovorin to treat colorectal cancer. When leucovorin and methotrexate are used together, this therapy often is called leucovorin rescue because leucovorin rescues healthy cells from the toxic effects of methotrexate. In patients with colorectal cancer, however, leucovorin increases the anti-cancer effect of fluorouracil.

Leucovorin also is used to treat megaloblastic anemia, a blood disorder in which red blood cells become larger than normal, and to treat accidental overdoses of drugs such as methotrexate.

Description

Leucovorin is a faster acting and stronger form of **folic acid**, and has been used for several decades. Folic acid also is known as vitamin B9, and is needed for the normal development of red blood cells. In humans, dietary folic acid must be reduced metabolically to tetrahydrofilic acid (THFA) to exert its vital biochemical functions. The coenzyme THFA and its subsequent other cofactors participate in many important reactions including DNA synthesis.

Leucovorin rescue

Some chemotherapy drugs, such as methotrexate (Mexate, Folex), work by preventing cells from using folic acid. Methotrexate therapy causes cancer cells to develop a folic acid deficiency and die. However, normal cells also are affected by folic acid deficiency. As a result, patients treated with drugs such as methotrexate often develop blood disorders and other toxic side effects. When these patients are given leucovorin, it goes into normal cells and rescues them from the toxic effects of the methotrexate. Leucovorin cannot enter cancer cells, however, and they continue to be killed by methotrexate. Leucovorin also works by rescuing healthy cells in patients who take an accidental overdose of drugs similar to methotrexate.

KEY TERMS

Folic acid—Vitamin B9.

Leucovorin rescue—A cancer therapy where the drug leucovorin protects healthy cells from toxic chemotherapy.

Combination therapy

Patients with colorectal cancer frequently are treated with fluorouracil (Adrusil). Fluorouracil, commonly called 5-FU, is effective, but only works for a short time once it is in the body. Leucovorin enhances the effect of fluorouracil by increasing the time that it stays active. As a result, the combination of the two drugs produces a greater anti-cancer effect than fluorouracil alone.

Recommended dosage

Leucovorin can be given as an injection, intravenously, or as oral tablets. For rescue therapy, leucovorin usually is given intravenously or orally within 24 hours of methotrexate treatment. Dosage varies from patient to patient. When used in combination with fluorouracil, leucovorin is given to the patient intravenously first, followed by fluorouracil treatment. To treat unintentional folic acid antagonist overdose, leucovorin is usually given intravenously as soon as possible after the overdose. Patients with megaloblastic anemia receive oral leucovorin.

Precautions

Patients with anemia, or any type of blood disorder, should tell their doctors. Leucovorin can treat only anemia caused by folic acid deficiency. Patients with other types of anemia should not take leucovorin. The effect of leucovorin on the fetus is not known, and it is not known if the drug is found in breast milk. Leucovorin should therefore be used with caution during pregnancy. Elderly patients treated with leucovorin and fluorouracil for advanced colorectal cancer are at greater risk for developing severe side effects.

Side effects

The vast majority of patients do not experience side effects from leucovorin therapy. Side effects are usually caused by the patient's chemotherapy, not by leucovorin. In rare cases, however, some patients can develop allergic reactions to the drug. These include skin rash, hives, and **itching**. In 2004, Swiss researchers found that oral desensitization may work in cases of severe allergic reaction to leucovorin.

Interactions

Although there are no listed drug interactions for leucovorin, patients should tell their doctors about any over the counter or prescription medication they are taking, particularly medication that can cause seizures.

Resources

PERIODICALS

"Oral Desensitization May Work in Some Cases of Allergy to Leucovorin." *Drug Week* November 14, 2003: 128.

Alison McTavish, M.Sc.
Teresa G. Odle

Leukapheresis *see* **Pheresis**

Leukemia *see* **Acute leukemia; Acute erythroblastic leukemia; Acute lymphocytic leukemia; Acute myelocytic leukemia; Chronic leukemia; Chronic lymphocytic leukemia**

Leukoencephalopathy

Description

Leukoencephalopathy is a disease occurring primarily in the white matter of the brain that involves defects in either the formation or the maintenance of the myelin sheath, a fatty coating that protects nerve cells. Leukoencephalopathy has several different forms and causes.

The symptoms of leukoencephalopathy reflect the mental deterioration that occurs as, at multiple sites within the brain, the myelin cover of nerve cells is eroded, leaving nerve cells exposed and with no protective insulation. Patients may exhibit problems with speech and vision, loss of mental function, uncoordinated movements, and extreme weakness and **fatigue**. Patients may have no desire to eat. The disease is usually progressive; patients continue to lose mental function, may have seizures, and finally lapse into a coma before death. Some patients stabilize, however, although loss of neurologic function is usually irreversible.

Leukoencephalopathy as it relates to cancer patients is primarily associated with **methotrexate chemotherapy**, which is used in treatment of many different types of cancer. Some other medications, including **cytarabine**, **fludarabine**, **carmustine** and **fluorouracil** in conjunction with **levamisole**. The disease may appear years

after the administration of methotrexate. Although rare, the incidence of leukoencephalopathy is increasing, as stronger drugs are developed and increased survival times allow time for the side effects of the treatments to appear.

A devastating type of leukoencephalopathy, called multifocal, or disseminated, necrotizing leukoencephalopathy, has been shown to occur primarily when methotrexate or cytarabine therapy is used in conjunction with a large cumulative dose of whole head irradiation. This disease is characterized by multiple sites of necrosis of the nerve cells in the white matter of the brain, involving both the myelin coating and the nerve cells themselves. Although some patients may stabilize, the course is usually progressive, with patients experiencing relentless mental deterioration and, finally, death.

Although leukoencephalopathy is primarily associated with methotrexate therapy, this disease has also been observed in association with other chemotherapeutic drugs (like intrathecal cytarabine) and occasionally been reported in association with cancers that have not yet been treated.

Another, particularly lethal, type of leukoencephalopathy called progressive multifocal leukoencephalopathy (PML) is an opportunistic infection that occurs in cancer patients who experience long-term immunosuppression as a result of the cancer (as in leukemia or **lymphoma**) or as a result of chemotherapy or immunosuppressive drugs. PML results when, due to chronic immunosuppression, the JC virus, widely found in the kidneys of healthy people, becomes capable of entering the brain. The virus infects the cells that produce myelin and causes multiple sites in the brain of nerve cells without the protective fatting coating. For reasons that are not completely clear, PML has a rapid and devastating clinical course, with death occurring typically less than six months after diagnosis.

Causes

It is only relatively recently that longer survival times for cancer patients have enabled scientists to identify an association of leukoencephalopathy with intensive chemotherapy (particularly methotrexate), especially when combined with large doses of whole head radiation. The causes of the neural degeneration observed are still not completely understood.

Most cases of leukoencephalopathy observed have occurred in patients who received methotrexate (either directly into the brain, through a tube in the skull, or intravenously) or who have received large doses of radiation to the head. Up to 50% of children who have received both treatments have developed necrotizing leukoencephalopathy, which differs from regular leukoencephalopathy in that the multiple sites of demyelinization also involve necrosis (the death of cells due to the degradative action of enzymes). Deterioration of the nerve tissue in necrotizing leukoencephalopathy appears to begin with the nerve and then spread into the myelin coating.

The method of action in PML is also not well understood. Long-term immunosuppression somehow appears to create an environment where the JC virus that inhabits most healthy human kidneys can mutate into a form that gains access to the brain. When in the brain, the virus infects and kills the cells that produce the myelin that forms a protective coating around the nerve.

Treatments

Unfortunately, there is no cure for any form of leukoencephalopathy, and no treatments approved. Although some medications have shown some effect against the deterioration involved in this disease, those identified have been highly toxic themselves, and none so far have been effective enough to justify use. The treatment of people with this disorder, therefore, tends to concentrate on alleviating discomfort.

Since there are no effective treatments, prevention must be emphasized. As the risks of certain treatment choices have become more defined, physicians must pursue careful treatment planning to produce optimal chance of tumor eradication while avoiding increased risk of the onset of a fatal and incurable side effect. This is especially true in children. The cases observed have largely been in children, which implies that the developing brain is at higher risk of developing treatment-associated leukoencephalopathy.

Alternative and complementary therapies

There are no commonly used alternative treatments, although since the disease is incurable, there is little risk involved in trying nontraditional medications. Complementary therapies (yoga, t'ai chi, etc.) that improve patient well being are appropriate if the patient finds them helpful.

Resources

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"Progressive Multifocal Leukoencephalopathy." *A Healthy Me*. [cited July 5, 2005]. <http://www.ahealthyme.com/article/gale/100083914>.

Wendy Wippel, M.Sc.

Leuprolide acetate

Definition

Leuprolide acetate is a synthetic (man-made) hormone that acts similarly to the naturally occurring gonadotropin releasing hormone (GnRH). It is available under the tradename Lupron.

Purpose

Leuprolide acetate is used primarily to counter the symptoms of advanced **prostate cancer** in men when surgery to remove the testes or estrogen therapy is not an option or is unacceptable to the patient. It is often used to ease the pain and discomfort of women suffering from endometrosis, advanced **breast cancer**, or advanced **ovarian cancer**.

Two less common uses of this drug are the treatment of **anemia** caused by bleeding uterine fibroids, and the treatment of early onset (precocious) puberty.

Description

Leuprolide acetate is a man-made protein that mimics many of the actions of gonadotropin releasing hormone. In men, it decreases blood levels of the male hormone **testosterone**. In women, it decreases blood levels of the female hormone estrogen.

Recommended dosage for prostate cancer

In men, there are three methods of dosing: daily injections, a monthly injection, or an annual implanted capsule. In the case of daily injections, 1 mg of leuprolide acetate is injected under the skin (subcutaneously). In the case of monthly injections, an implanted capsule that contains 7.5 mg of leuprolide acetate is injected into a muscle. In the case of an annual implanted capsule, the capsule contains 72 mg of leuprolide acetate. Both the monthly and the annual capsules are specially designed to slowly release the drug into the patient's bloodstream over the specified time. The monthly capsule dissolves completely over the course of the month. The annual capsule must be removed after 12 months.

In the case of self-administered daily injections, a patient who misses a dose should take that dose as soon as it is noticed. However, if he or she does not remember until the next day, the missed dose should be skipped. Dosages should not be doubled.

Precautions

People taking leuprolide acetate should not drive a car, cook, or engage in any activity that requires alertness until they have been taking the medication long enough to be sure how it affects them.

Leuprolide acetate may cause birth defects if taken during pregnancy, and may be passed to an infant via breast milk. Therefore, women who are pregnant or nursing should not take leuprolide acetate without first consulting their doctors.

Leuprolide acetate will also interfere with the chemical actions of birth control pills. For this reason, sexually active women who do not wish to become pregnant should use some form of birth control other than birth control pills.

Side effects

In patients of both sexes, common side effects of leuprolide acetate include:

- tumor flare, which is exhibited as **bone pain** (due to a temporary initial increase in testosterone/estrogen before its production is finally decreased)
- sweating accompanied by feelings of warmth (hot flashes)
- lack of energy (lethargy)
- depression, or other mood changes
- headache
- enlargement of the breasts
- decreased sex drive

Other common side effects in women include:

- light, irregular vaginal bleeding
- no menstrual period
- pelvic pain
- vaginal dryness and/or **itching**
- emotional instability
- increase in facial or body hair
- deepening of the voice

Less common side effects, in patients of either sex, include:

- burning or itching at the site of the injection
- nausea and vomiting

KEY TERMS

Endometrial tissue—The tissue lining the uterus that is sloughed off during a woman's menstrual period.

Fibroid—A benign smooth muscle tumor of the uterus.

Gonadotropin releasing hormone (GnRH)—A hormone produced in the brain that controls the release of other hormones that are responsible for reproductive function.

Prostate gland—A small gland in the male genitals that contributes to the production of seminal fluid.

- insomnia
- weight gain
- swollen feet or lower legs
- constipation

Other side effects in men can include impotence and decreased testicle size.

A doctor should be consulted immediately if the patient experiences any of the above symptoms.

Interactions

There are no known interactions of leuprolide acetate with any food or beverage. People taking leuprolide acetate should consult their physician before taking any other prescription drug, over-the-counter drug, or herbal remedy. People currently taking any other hormone or steroid-based medications should not take leuprolide acetate without first consulting their physician.

See also Endometrial cancer.

Paul A. Johnson, Ed.M.

Levamisole

Definition

Levamisole is used to treat **colon cancer**, specifically stage III colon cancer. Levamisole takes the full name of levamisole hydrochloride, and it is also known by the brand name Ergamisol.

Purpose

Levamisole is used to treat patients with stage III colon cancer after they have had surgery to remove the tumor, or as much of the tumor as possible. In stage III colon cancer, the cancer has spread to nearby lymph nodes. Levamisole is approved for use with **fluorouracil** (specifically, 5-fluorouracil), a drug that is thought to prevent cells from replicating, or making more of themselves, by interfering with the manufacture of the hereditary material the cells carry. The use of levamisole with fluorouracil makes it an adjuvant therapy, or one that when used in conjunction with another drug seems to increase the defenses of the patient.

Description

Levamisole was first made (by laboratory synthesis) in 1966, and since then it has been used in veterinary medicine to eliminate intestinal, or lower gut, parasites in domestic animals. It was found to be immunostimulant in 1972 and approved for use for colon cancer in 1990.

The drug seems to have a number of benefits for the patient. It increases the response of T cells, or cells belonging to the lymphatic system that can fight cancer cells. It also seems to increase the activity of cells that attack and destroy invading or cancer cells, including both monocytes and macrophages.

Because of the response levamisole brings from T cells, causing them to be more active, it falls into the category of drugs known as biological response modifiers.

Recommended dosage

The drug is given orally in tablet form. Tablets contain 50 milligrams of levamisole hydrochloride, and a standard dose is one tablet every eight hours for three days. Thereafter, the patient takes the same three-day course every two weeks for about a year.

Dosage must be adjusted according to the count of white blood cells and platelets in a patient's blood. In some cases, levamisole can be continued, even when fluorouracil must be stopped.

Precautions

The drug can cause changes in the composition of the blood, which can be fatal. For example, agranulocytosis, also known as **neutropenia**, may develop. The condition refers to a drop in a kind of white blood cells known as neutrophils that are important in the defense against bacteria and fungus. Thus, the patient becomes more likely to get a bacterial or fungal infection.

KEY TERMS

Adjuvant therapy—Addition of a drug to another course of drug therapy to increase or enhance the immune response of a patient.

Macrophage—Large cell-eating cell.

Monocyte—A specialized type of white blood cell that attacks other cells, and acts as a phagocyte.

Neutrophil—A specialized type of white blood cell that attacks other cells, and acts as a phagocyte.

Parasite—An organism that lives by taking its nourishment from another organism.

Phagocyte—Cell-eating cell.

T cell—A cell in the lymphatic system that contributes to immunity by attacking foreign bodies, such as bacteria and viruses, directly.

Side effects

Nausea and vomiting, **diarrhea**, hair loss (**alopecia**), and changes in the composition of the white blood cells, such as neutropenia, are among the most common side effects.

Interactions

Levamisole often interacts with alcohol in the same way that the drug disulfiram, which is used to discourage **alcohol consumption** in alcoholics (alcohol deterrent), does. The reaction is extremely unpleasant, and alcohol use is best avoided when levamisole is being taken.

The drug also interacts with **warfarin**, which is often given to heart patients to reduce the chance of blood clots forming. Levamisole can interfere with the action of warfarin, allowing blood clots to form; therefore, adjustments in the amount of warfarin heart patients take may be necessary if they are also taking levamisole.

Diane M. Calabrese

Li-Fraumeni syndrome

Definition

Li-Fraumeni syndrome (LFS) is a genetic disorder caused by a hereditary mutation in a cancer susceptibility gene. Individuals with LFS have an increased risk for developing certain types of cancer, often at younger ages than is typically observed in the general population.

Description

Li-Fraumeni syndrome (LFS) was first described by Dr. Frederick Li and Dr. Joseph Fraumeni in 1969. It is caused by mutations in the TP53 gene, located on chromosome 17. The types of mutations that cause LFS are known as hereditary mutations, and therefore can be inherited, or passed from a parent to a child.

Cancer risks

The TP53 gene is a tumor suppressor gene. When an individual inherits a mutation in this type of gene from one of his or her parents, there is an increased risk for developing certain kinds of cancer. The most common kinds of cancer associated with LFS are sarcomas, or tumors that arise in connective tissue, like bone or cartilage.

Females with LFS have an increased risk for developing **breast cancer**. Males and females may also be at risk for developing leukemia, **melanoma**, colon, pancreatic, and brain cancer. They may also develop adrenalcorticoid tumors, which develop on the outer surface of the adrenal glands. These cancers often occur at younger ages than are typically observed in the general population, often before age 45.

Some individuals with LFS may develop certain cancers, such as brain tumors, sarcomas, or adrenalcorticoid tumors in childhood. In addition, individuals with a mutation in the TP53 gene have a higher risk for developing multiple primary cancers. For example, a person with LFS who develops a sarcoma at a young age and survives that cancer has an increased risk for developing a second, or possibly even a third different kind of cancer.

Genetic counseling and testing

Genetic testing for mutations in the TP53 gene is usually performed on a blood sample from the relative in the family who has had one of the cancers associated with LFS at a young age. One of the most effective ways to test for mutations in the TP53 gene is by sequencing, a process whereby the chemical components of a patient's DNA is compared to that of DNA that is known to be normal. If the entire DNA code of the TP53 gene is sequenced, it is believed that the majority (98%) of the (mutations) that are responsible for Li-Fraumeni syndrome can be identified. However, as the process of sequencing is a difficult and often time-consuming

Age of onset for cancers associated with Li-Fraumeni syndrome

Age of onset	Type of cancer
Infancy	Development of adrenocortical carcinoma
Under five years of age	Development of soft-tissue sarcomas
Childhood and young adulthood	Acute leukemias and brain tumors
Adolescence	Osteosarcomas
Twenties to thirties	Premenopausal breast cancer is common

process, it is not always performed for every patient. Often, only specific areas of the TP53 gene, where there is most likely to be a mutation associated with LFS, are analyzed. The length of time to receive results depends on the extent of testing that is performed and the laboratory that is used.

Due to the fact that some of the cancers associated with LFS can occur at very young ages, there is a question as to whether genetic testing should be an option for at-risk children. Typically, genetic testing is not offered to anyone under the age of 18. However, because there are some screening options available for children with LFS, it is thought that the option of testing could not be denied if a parent feels that it is important for his or her son or daughter's future health. Groups such as the National Society of Genetic Counselors are beginning to explore the issue of genetic testing in minors (those under age 18) for mutations in cancer susceptibility gene, especially if these minors would be at risk for developing **childhood cancers**.

It is important to understand the various categories of results that are associated with undergoing genetic testing for mutations in the TP53 gene. A positive result indicates the presence of a genetic mutation that is known to be associated with an increased risk for developing the types of cancer associated with LFS. Once this kind of mutation has been found in an individual, it is possible to test this person's relatives, such as the children, for the presence or absence of that particular mutation. Individuals who have a mutation in the TP53 gene have a 50% chance of passing on this mutation to their children.

Even if a patient has a mutation in the TP53 gene, it does not mean that he or she will definitely develop one of the cancers that are associated with Li-Fraumeni. However, the risk for those with the mutation is much higher than for someone in the general population. The likelihood that a person will develop cancer if they have a mutation in a cancer susceptibility gene like TP53 is called penetrance.

If the first person tested within a family is not found to have an alteration in the TP53 gene, his or

KEY TERMS

Adrenalcorticoid tumors—Cancer that arises on the outer surface of the adrenal glands.

Adrenal glands—Structures located on top of the kidneys that secrete hormones.

Cancer—The process by which cells grow out of control and subsequently invade nearby cells and tissue.

Cancer susceptibility gene—The type of genes involved in cancer. If a mutation is identified in this type of gene it does not reveal whether or not a person has cancer, but rather whether an individual has an increased risk (is susceptible) to develop cancer (or develop cancer again) in the future.

Chromosome—Structures found in the center of a human cell on which genes are located.

Gene—Packages of DNA that control the growth, development and normal function of the body.

Genetic counselor—A specially trained health care provider who helps individuals understand if a disease (such as cancer) is running in their family and their risk for inheriting this disease. Genetic counselors also discuss the benefits, risks and limitations of genetic testing with patients.

Leukemia—Cancer that arises in blood cells.

Mammogram—A screening test that uses x rays to look at a woman's breasts for any abnormalities, such as cancer.

Mutation—An alteration in the number or order of the DNA sequence of a gene.

Penetrance—The likelihood that a person will develop a disease (such as cancer), if he or she has a mutation in a gene that increases the risk for developing that disorder.

Sarcoma—Cancer that occurs in connective tissue, such as cartilage or bone.

Sequencing—A method of performing genetic testing where the chemical order of a patient's DNA is compared to that of normal DNA.

Tumor suppressor gene—Genes that typically prevent cells from growing out of control and forming tumors that may be cancerous.

Ultrasound—A test that uses sound waves to examine organs in the body

QUESTIONS TO ASK THE DOCTOR

- What is the likelihood that the cancer in my family is due to a mutation in a cancer susceptibility gene, particularly the TP53 gene?
- If my family is found to have Li-Fraumeni syndrome, what is the chance that I carry a mutation in the TP53 gene?
- What are the benefits, limitations and risks of undergoing genetic testing?
- What is the cost of genetic testing and how long will it take to obtain results?
- If I undergo genetic testing, will my insurance company pay for testing? If so, will I want to share my results with them?
- What does a positive test result mean for me?
- What does a negative test result mean for me?
- If I test positive for a mutation in a cancer susceptibility gene, what are the best options available for screening and prevention? What research studies may I be eligible to participate in?
- What legislation is in effect to protect me against discrimination by my insurer or employer?

her result is negative. Often this result is called indeterminate, because a negative test result cannot completely rule out the possibility of hereditary cancer being present within a family. The interpretation of this type of result can be very complex. For example, a negative result may mean that the method used to detect mutations in the TP53 gene may not be sensitive enough to identify all mutations. Additionally, the mutation might be located in a part of the gene that is difficult to analyze. It may also mean that a person has a mutation in another cancer susceptibility gene that has not yet been discovered or is very rare. Finally, a negative result could mean that the person tested does not have an increased risk for developing cancer because of a mutation in a single cancer susceptibility gene.

Screening and prevention options

With the exception of screening for breast cancer, there are no effective means to screen for and/or prevent the cancers that are associated with Li-Fraumeni syndrome. However, researchers have developed some screening guidelines for those with LFS. For men and women, it is recommended that they undergo a thorough physical exam with their doctor every year. This should include skin and **colon cancer** screening along with a complete exam of the nervous system. Women should also undergo breast cancer screening, which consists of annual mammograms, self-breast exams, and breast exams by a physician or health care provider. Individuals with Li-Fraumeni syndrome may choose to undergo screening more often and at an earlier age then people in the general population.

For children with a TP53 mutation, it is recommended that they also undergo a complete physical exam once a year by their physician. This should include an analysis of their urine and blood and an abdominal ultrasound.

See also Genetic testing.

Resources

ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800)ACS-2345. <http://www.cancer.org>.

National Cancer Institute. 31 Center Dr., MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. <http://www.nci.nih.gov>.

National Society of Genetic Counselors. 233 Canterbury Dr., Wallingord, PA 19086-6617. (610) 872-7608. <http://www.nsgc.org>.

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Tiffani A. DeMarco, M.S.

Limb salvage

Definition

Limb salvage is a type of surgery that removes a cancerous tumor or lesion while preserving the nearby muscles, tendons, and blood vessels.

Purpose

Doctors perform limb salvage to remove cancer and avoid **amputation**, while preserving the patient's appear-

ance and the greatest possible degree of function in the affected limb. The procedure is most commonly performed for bone tumors and bone **sarcomas**, but is also commonly performed for soft tissue sarcomas affecting the extremities.

This complex alternative to amputation is used to cure cancers that are slow to spread from the limb where they originate to other parts of the body, or that have not invaded soft tissue.

Precautions

Limb salvage should only be performed by experienced surgeons with specialized expertise. It should also be limited to cases in which the surgery would restore more and longer-lasting function than could be achieved by amputating the affected limb and fitting the patient with an artificial replacement (prosthesis).

If the cancer's location makes it impossible to remove the malignancy without damaging or removing vital organs, essential nerves, key blood vessels, or if it is impossible to reconstruct a limb that will function satisfactorily, salvage surgery may not be an appropriate treatment.

Biopsy is a critical component of limb-salvage surgery. A poorly planned or improperly performed biopsy can limit the patient's surgical options and make amputation unavoidable.

Description

Also called limb-sparing surgery, limb salvage involves removing the cancer and about an inch of healthy tissue surrounding it, and, if bone was removed, replacing the removed bone. The replacement can take the form of synthetic metal rods or plates (prostheses), pieces of bone (grafts) taken from the patient's own body (autologous transplant), or pieces of bone removed from a donor body (cadaver) and frozen until needed for transplant (allograft). In time, transplanted bone grows into the patient's remaining bone. **Chemotherapy**, radiation, or a combination of both treatments may be used to shrink the tumor before surgery is performed.

Stages of surgery

Limb salvage is performed in three parts. Doctors remove the cancer and a margin of healthy tissue, implant a prosthesis or bone graft (when necessary), and close the wound by transferring soft tissue and muscle from other parts of the patient's body to the surgical site. This treatment cures some cancers as successfully as amputation.

Surgical techniques

BONE TUMORS Doctors remove the malignant lesion and a cuff of normal tissue (wide excision) to cure low-grade tumors of bone or its components. To cure high-grade tumors, they also remove muscle, bone, and other tissues affected by the tumor (radical resection).

SOFT TISSUE SARCOMAS Doctors use limb-sparing surgery to treat about 80% of soft tissue sarcomas affecting extremities. The surgery removes the tumor, lymph nodes or tissues to which the cancer has spread, and at least one inch of healthy tissue on all sides of the tumor.

Radiation and/or chemotherapy may be administered before or after the operation. Radiation may also be administered during the operation by placing a special applicator against the surface from which the tumor has just been removed, and inserting tubes containing radioactive pellets at the site of the tumor. These tubes remain in place during the operation and are removed several days later.

To treat a soft tissue sarcoma that has spread to the patient's lung, the doctor may remove the original tumor, administer radiation or chemotherapy treatments to shrink the lung tumor, and surgically remove the lung tumor.

Limb salvage for children

Doctors use expandable prostheses to perform limb-salvage surgery on children who have not stopped growing (skeletal immaturity). These children may need as many as four additional operations, at intervals of six to 12 months, to expand the prostheses as their limbs lengthen.

Because expandable prostheses have been available only since the 1980s, the long-term effects of using them are unknown.

Preparation

Before deciding that limb salvage is appropriate for a particular patient, the doctor considers what type of cancer the patient has, the size and location of the tumor, how the illness has progressed, and the patient's age and general health.

After determining that limb salvage is appropriate for a particular patient, the doctor makes sure that the patient understands what the outcome of surgery is likely to be, that the implant may fail, and that additional surgery—even amputation—may be necessary.

Preoperative rehabilitation

Physical and occupational therapists help prepare the patient for surgery by introducing the muscle-strengthening, ambulation, and range of motion (ROM) exercises the patient will begin performing right after the operation.

Aftercare

During the five to ten days the patient remains in the hospital following surgery, nurses monitor sensation and blood flow in the affected extremity and watch for signs that the patient may be developing **pneumonia**, pulmonary embolism, or deep-vein thrombosis.

The doctor prescribes broad-spectrum **antibiotics** for at least the first 48 hours after the operation and often prescribes medication (prophylactic anticoagulants) and antiembolism stockings to prevent blood clots. A drainage tube placed in the wound for the first 24–48 hours prevents blood (hematoma) and fluid (seroma) from accumulating at the surgical site. As postoperative pain becomes less intense, mild narcotics or anti-inflammatory medications replace the epidural catheter or patient-controlled analgesic pump used to relieve pain immediately after the operation.

Exercise intervention

Limb salvage requires extensive surgical incisions, and patients who have these operations need extensive rehabilitation. The amount of bone removed and the type of reconstruction performed dictate how soon and how much the patient can exercise, but most patients begin muscle-strengthening, continuous passive motion (CPM), and ROM exercises the day after the operation and continue them for the next 12 months.

A patient who has had upper-limb surgery can use the opposite side of the body to perform hand and shoulder exercises. Patients should not do active elbow or shoulder exercises for two to eight weeks after having surgery involving the bone between the shoulder and elbow (humerus). Rehabilitation following lower-extremity limb salvage focuses on strengthening the muscles that straighten the legs (quadriceps), maintaining muscle tone, and gradually increasing weight-bearing so that the patient is able to stand on the affected limb within three months of the operation. A patient who has had lower-extremity surgery may have to learn a new way of walking (gait retraining) or wear a lift in one shoe.

Goals of rehabilitation

Physical and occupational therapy regimens are designed to help the patient move freely, function independently, and accept changes in **body image**. Even patients who look the way they did before surgery are likely to feel that the operation has altered their appearance.

Before a patient goes home from the hospital or rehabilitation center, the doctor decides whether the patient needs a walker, brace, cane, or other device, and should make sure that the patient can climb stairs. Also, the doctor should emphasize the life-long importance of preventing infection and give the patient written instructions about how to prevent infection and what to do if infection does develop.

Risks

The major risks associated with limb salvage include superficial or deep infection at the site of the surgery; loosening, shifting, or breakage of implants; rapid loss of blood flow or sensation in the affected limb; and severe blood loss and **anemia** from the surgery.

Postoperative infection is a serious problem. Chemotherapy or radiation can weaken the immune system, and extensive bone damage can occur before the infection is identified. Tissue may die (necrosis) if the surgeon used a large piece of tissue (flap) to close the wound. This is most likely to occur if the surgical site was treated with radiation before the operation. Treatment for postoperative infection involves removing the graft or implant, inserting drains at the infected site, and giving the patient oral or intravenous antibiotic therapy for as long as 12 months. Doctors may have to amputate the affected limb.

Normal results

A patient who has had limb-sparing surgery will remain disease-free as long as a patient whose affected extremity has been amputated.

Salvaged limbs always function better than artificial ones. However, it takes a year for patients to learn to walk again following lower-extremity limb salvage, and patients who have undergone upper-extremity salvage must master new ways of using the affected arm or hand.

Successful surgery reduces the frequency and severity of patient falls and of the fractures that often result from disease-related changes in bone. Although successful surgery results in limbs that look and function very much like normal, healthy limbs, it is not unusual for patients to feel that their appearance has changed.

Abnormal results

Some patients will need additional surgery within five years of the first operation. Some will eventually require amputation.

Post-operation directives from the patient's physician may include the following items:

- Patients may be told that they should never jog, lift heavy objects, or play racquet sports.

QUESTIONS TO ASK THE DOCTOR

- Why do you think limb salvage will be successful in my case?
- How will I look and feel after the operation?
- Will I be able to enjoy my favorite sports and other activities after the operation?

- Wearing a splint or cast can damage nerves and veins in the affected limb.
- Implants can loosen, shift to a new position, or break.

See also Chondrosarcoma; Ewing's sarcoma; Osteosarcoma.

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Maureen Haggerty

Lip cancers

Definition

Lip cancer is a malignant tumor, or neoplasm, that originates in the surface layer cells of the epithelial tissue in the upper or lower lip.

Description

The upper and lower lips are the well-defined red (often called vermilion) areas that surround the opening to the mouth. They contain muscles and special cells (receptors) that are sensitive to heat and cold and feeling. Largely taken for granted, the lips are important in identifying types of food to the brain and in getting food into the mouth. Lips also play a crucial role in speech.

A malignant tumor, or neoplasm, that originates in the cells of one of the lips is a cancer of the lip. Lip cancer almost always begins in the flat, or squamous, epithelial cells. Epithelial cells form coverings (tissues) for the surfaces of the body. Skin, for example, has an outer layer of epithelial tissue.

If a part of the lip is affected by cancer and must be removed by surgery, there will be significant changes in eating ability and speech function. The more lip tissue removed, the greater the disturbances to the normal patterns of talking and eating.

Demographics

Nine out of ten cases of lip cancer are diagnosed in people over the age of 45. Age, or the aging process, may contribute to the way the cancer develops. As a line of cells gets older, the genetic material in a cell loses some of its ability to repair itself. When the repair system is operating normally, damage to the genetic material, or DNA, caused by ultraviolet light from the sun is quickly weeded out. When the system fails, changes in the genetic material are kept, and they multiply when a cell divides.

If the genetic material cannot repair itself, damage caused by exposure to environmental factors such as sunlight and chemicals can quickly set in motion the uncontrolled growth of cells.

The effects of factors that are known to cause lip cancer, such as smoking and exposure to sunlight, also add up as a person ages. Thus, the combination of a breakdown in the repair system in the genetic material and the considerable periods of time (decades) over which a person is exposed to cancer agents probably causes lip cancers. However, researchers are still investigating how lip cancers start.

Men are at greater risk for lip cancer than women. Depending on where they live, men are two or three times more likely to be diagnosed than women. Fair-skinned people are more likely to get lip cancer than those with dark skin. For reasons not yet understood, people in Asia have a much lower risk of lip cancer than those living on other continents. In many parts of Asia, lip cancer is extremely rare. In North America, nearly 13

out of 100,000 men will be diagnosed with lip cancer during their lifetime. In Australia, about 13.5 men per 100,000 will be diagnosed.

The frequency of lip cancer is often lumped together with oral cancer, although lip cancer is probably much more like skin cancer in origin. There are about 30,000 new diagnoses of mouth and lip cancer in the United States each year. About 38% percent of all cancers of the mouth begin in the lower lip; on the other hand, cancers of the upper lip are more aggressive than those of the lower lip.

In some places, such as South Australia, women are experiencing a striking increase in lip cancer diagnoses. There are several theories to explain the trend. Among them, perhaps fewer women regularly wear hats, which offer protection from the sun. Women might also be forgoing lipstick, which serves as another barrier to sunlight.

Causes and symptoms

Exposure to sunlight and smoking, particularly pipe smoking, increases the risk of developing lip cancer. However, the way they do so is not understood. Alcohol consumption is tied to **oral cancers** and may contribute to lip cancer as well.

Much of the evidence about the link between time spent in the sun and lip cancer comes from a look at those who are most likely to be diagnosed. Among them are farmers, golfers, and others who spend long periods of time outdoors.

Lip cancer seems to share some properties with skin cancer in the way it originates. Yet several studies suggest that it takes more than exposure to sun to increase the risk of lip cancer. Viral infection is a risk factor, as is reduced immunity, which is a condition that may be caused by viral infection. A team of researchers in the Netherlands recently reported a link between liver transplants and a higher risk of lip and skin cancer following the transplant. The results are not unexpected. In this procedure, drugs are used to suppress, or lower, the activity of a recipient's immune system so that a donor organ will be accepted. Thus, the immunity of the organ recipient is low, and lower immunity is linked to lip cancer.

Individuals with acquired immunodeficiency syndrome (AIDS) are at a greater risk for lip cancer. People infected with **herpes simplex** viruses, papilloma viruses and other viruses may also be at greater risk.

Vitamin deficiency may also be a factor that contributes to lip cancer. The sorts of **vitamins** found in fruits and vegetables, particularly carotene, the substance the body uses to form vitamins A and C, seem to be important in preventing lip cancer.

Particular symptoms of this cancer include white spots, sores, or lumps on the lip. Pain can also be a symptom, particularly pain in a lymph node near the affected part of the lip. This is a troubling symptom, since it indicates that the cancer has metastasized (spread) beyond the lip.

Diagnosis

Dentists frequently identify a suspicious spot, sore, or lump on the lip. A good dental exam includes an examination of the lips and the mouth. **X ray** and **biopsy**, the taking of a tissue sample for analysis, can be used to determine whether or not cancer is present.

Because spots and sores on the lips can be short-lived, people should not be alarmed by every change that appears. However, when there is a change that occurs and stays, it should be investigated. If the next scheduled dental visit is several months away, a special appointment with the dentist or a physician should be made. Dentists should tell their patients, particularly older ones, how to undertake a regular self-exam of the lips between check-ups.

Treatment team

A physician who specializes in oncology, the study and treatment of cancer, will probably take the lead on treatment. A surgeon will remove the cancer. Not all oncologists are surgeons, so it is likely that the team will include a medical oncologist, who coordinates treatment, as well as a surgical oncologist, who performs the surgery.

Because surgery on the lip can interfere with eating and talking, most teams include a nutritionist and a speech pathologist. Scars and alterations of facial features can produce changes in **body image**, and a psychiatrist or social worker may participate in the team to help a patient cope with such changes. It is possible that a dentist or oral surgeon will also play a role. Nurses who administer **chemotherapy** and monitor the status of patients will be involved, as will radiation technicians and a radiation oncologist. If reconstruction of a lip is necessary because of the amount of tissue removed or the size of a scar, a plastic surgeon will be added to the team.

Clinical staging, treatments, and prognosis

The ability to see a suspicious area on the lips and to detect lip cancer early combine to form the staging process. (One inch equals 2.5 cm.)

- Stage I: The cancer is less than one inch in diameter and has not spread.
- Stage II: The cancer is up to approximately two inches in diameter and has not spread.
- Stage III: The cancer is either larger than two inches or has spread to a lymph node on the side of the neck that matches the primary location of the lip cancer. The lymph node is enlarged, but not much more than an inch.
- Stage IV: One or more of several things can occur. There may be a spread of cancer to the mouth or to the areas around the lip, more than one lymph node with cancer, or **metastasis** (spread) to other parts of the body.

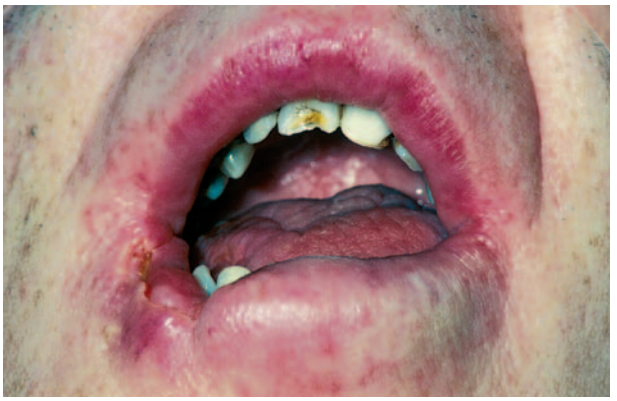
The outlook for recovery from lip cancer is very good if it is diagnosed early. For stage I and stage II cancers, surgery to remove the cancer or radiation treatment of the affected area is sometimes all that is required to produce a cure. Decisions about which method to use depend on many factors, but the size of the tumor and the tolerance a patient has for radiation or chemotherapy are particularly important. The larger the tumor, the more urgent is its removal. Smaller tumors can be treated with radiation or other methods in an effort to shrink them before surgery. In some cases, surgery might be avoided. For stage III cancer with lymph node involvement, the cancerous lymph nodes are also removed.

Chemotherapy may be used at any stage, but it is particularly important for stage IV cancer. In some cases, chemotherapy is used before surgery, just as radiation is, to try to eliminate the cancer without cutting, or at least to make it smaller before it is cut out (excised). After surgery, **radiation therapy** and chemotherapy are both used to treat patients with stage IV lip cancer, sometimes in combination.

There are many new and promising types of treatment for lip cancer. For example, heat kills some cancer cells, and a treatment known as **hyperthermia** uses heat to eliminate cancer in some patients.

Because lip cancers are well-studied and often successfully treated, the best practices for dealing with the cancer, or a suspected cancer, are specific. In the case of how to extract and study tissue to determine whether a suspicious growth is malignant (biopsy), size is an extremely useful guide.

It is possible to take tissue from a suspected lip cancer for examination, or biopsy, by simply piercing and extracting tissue with a large, hollow needle. The technique is called a punch biopsy. However, the method is not recommended for any tumor that is thicker than about one-sixteenth of an inch. For thicker tumors, a tissue sample is better taken by cutting into the tumor, that is, making an incision.



Squamous cell carcinoma on lip. *(Custom Medical Stock Photo. Reproduced by permission.)*

The success with identifying lip cancer early and eliminating it means that it is not a big killer. Only 4 in 2.5 million people die from lip cancer each year, or about 112 individuals in the entire United States population. In contrast, cancers in the oral cavity, including on the tongue, cause more than 8,000 deaths in the United States each year.

Alternative and complementary therapies

Because there seems to be some link between a chronic absence of vitamins A and C in the diet and lip cancer, some complementary therapies promote taking massive amounts of the vitamins, or megavitamins. The value of such therapy has not been demonstrated. In order to avoid possible side effects or harmful interactions with standard cancer treatment, patients should always notify their treatment team of any over-the-counter or herbal remedies that they are taking.

Coping with cancer treatment

The doctor and patient should discuss the need for a way to communicate if speech is impaired after surgery. A pad and pencil may be all that is needed for a short interval. If there will be a long period of speech difficulty, patients should be ready with additional means, such as TYY phone service.

A change in appearance after the removal of a lip cancer can lead to concerns about body image, and social interaction may suffer. A support group can help. Discussions with a social worker, loved ones, or other patients who have undergone similar treatment can be of major benefit.

If a significant portion of lip is removed, speech therapy may be necessary to relearn how to make certain

KEY TERMS

Biopsy—A procedure in which a tissue sample is taken from the body for examination.

Epithelial tissue—The collection of cells that form coverings for the surfaces of the body.

Immunity—Ability to resist the effects of agents, such as bacteria and viruses, that cause disease.

Lymph node—A concentration of lymphatic tissue and part of the lymphatic system that collects fluid from around the cells and returns it to the blood vessels, and helps with the immune response.

Squamous cells—Flat epithelial cells, which usually make up the outer layer of epithelial tissue, the layer farthest away from the surface the epithelium covers.

QUESTIONS TO ASK THE DOCTOR

- Is this cancer curable?
- What is the stage of the cancer?
- What is the likelihood the cancer will recur?
- Is there a clinical trial in which I should participate?

sounds. Scars and alterations of the lips usually can be reduced or hidden entirely with the techniques available from plastic surgery, so any alteration in appearance because of lip cancer is typically transient.

Reconstruction of the lip will help with appearance, but it might not make it easier to talk, especially if muscle tissue is removed during the surgery to eliminate the cancer. In many cases, the reconstruction process actually damages more muscle and sensory tissue. New methods of **reconstructive surgery** are being developed to avoid such an outcome. Some of these newer methods involve grafts of skin and muscle taken from the forearm or the area of the cheek near the angle of the jawbone. In general, reconstruction of the lower lip is more difficult than reconstruction of the upper lip.

Appetite may be affected before, during and after treatment. Before treatment, the presence of a tumor can interfere with the tasting of food, and food might not seem as appealing as it once did. During treatment, particularly radiation treatment, the area of the lips and mouth might be sore and make eating difficult. After treatment, a loss of sensation in the part of the lip affected can reduce appetite. A nutritionist can help with supplements for those who experience significant **weight loss** and who do not have an appetite.

Clinical trials

The Cancer Information Service at the National Institutes of Health offers information about **clinical trials** that are looking for volunteers. The service can be reached at <http://cancertrials.nci.nih.gov> or (800) 422-6237.

Prevention

The best preventive measures are minimizing sun exposure and avoiding tobacco and alcohol. Eating plenty of fruits and vegetables is a good measure. Even though the importance of fruits and vegetables is not proven to prevent lip cancer, overall fruits and vegetables are demonstrated cancer-fighters. Any precaution that is taken against contracting human immunodeficiency virus (HIV), which causes AIDS, is also likely to reduce the chance of developing lip cancer.

Special concerns

Certain diseases can mimic a possible lip cancer. They must be ruled out if a suspicious spot is found. This is particularly true in areas where diseases that cause lesions, or sores, on the lips are found. One such disease is *histoplasmosis capsulatum*, which is caused by a fungus. It sometimes produces an ulcer, or lesion, on the lip that leads to suspicion of lip cancer.

Sometimes lip cancer cannot be cured. It may keep recurring. It may also metastasize, particularly to the lungs. But overall, lip cancer is considered highly curable. Talking openly with the physician in charge of care is important in order for the patient to understand the course of the disease and be prepared to make decisions.

See also Oropharyngeal cancer.

Resources

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American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS). 310 South Henry Street, Alexandria, VA 22314. (703) 299-9291. <www.facemd.org>.

American Society of Plastic Surgeons (ASPS). 444 East Algonquin Road, Arlington Heights, IL 60005. (847) 228-9900. <www.plasticsurgery.org>.

Support for People with Oral and Head and Neck Cancer (SPOHNC). P.O. Box 53, Locust Valley, NY 11560-0053. (800) 377-0928. <http://www.spohnc.org>.

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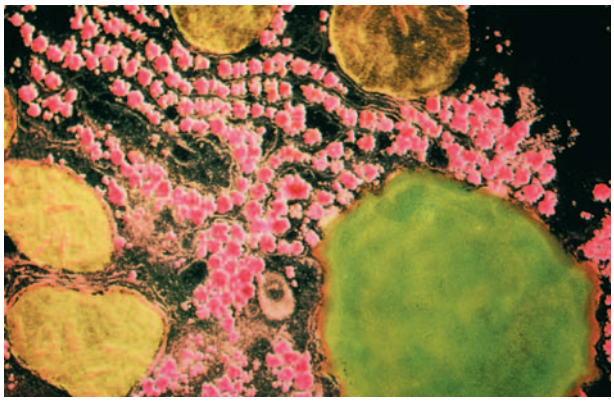
Liver biopsy

Definition

A liver **biopsy** is a medical procedure performed to obtain a small piece of liver tissue for diagnostic testing. Liver biopsies are sometimes called percutaneous liver biopsies, because the tissue sample is obtained by going through the patient's skin.

Purpose

A liver biopsy is usually done to diagnose a tumor, or to evaluate the extent of damage that has occurred to the liver because of chronic disease. Biopsies are often performed to identify abnormalities in liver tissues after **imaging studies** have failed to yield clear results.



A false-color scanning electron micrograph (SEM) of hepatocyte cells of the liver that secrete bile. *(Photograph by John Bavosi. Custom Medical Stock Photo. Reproduced by permission.)*

A liver biopsy may be ordered to evaluate any of the following conditions or disorders:

- jaundice
- cirrhosis
- hemochromatosis, which is a condition of excess iron in the liver
- repeated abnormal results from liver function tests
- unexplained swelling or enlargement of the liver
- primary cancers of the liver, such as hepatomas, cholangiocarcinomas, and angiosarcomas
- metastatic cancers of the liver

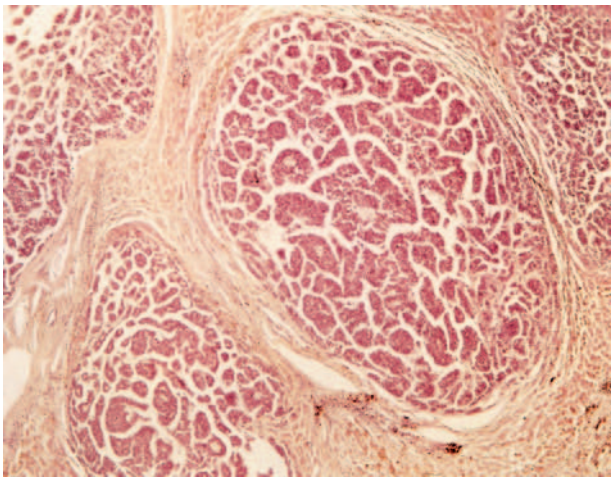
Precautions

Some patients should not have percutaneous liver biopsies. They include patients with any of the following conditions:

- a platelet count below 60,000
- a longer-than-normal prothrombin time
- a liver tumor that contains a large number of blood vessels
- a history of unexplained bleeding
- a watery (hydatid) cyst
- an infection in either the cavity around the lungs, or the diaphragm

Description

Percutaneous liver biopsy is done with a special hollow needle, called a Menghini needle, attached to a



Light micrograph of a section through a primary carcinoma from a human liver. Healthy liver cells are normally arranged in roughly hexagonal structures called lobules. In this cancerous liver, the lobules are disintegrating, and abnormal fibrous tissue has proliferated around them. *(Copyright John Burbridge, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

KEY TERMS

Biopsy—A procedure where a piece of tissue is removed from a patient for diagnostic testing.

Menghini needle—A special needle used to obtain a sample of liver tissue.

Percutaneous biopsy—A biopsy in which a needle is inserted and a tissue sample removed through the skin.

Prothrombin time—A blood test that determines how quickly a person's blood will clot.

Vital signs—A person's essential body functions, usually defined as the pulse, body temperature, and breathing rate.

suction syringe. Doctors who specialize in the digestive system or liver will sometimes perform liver biopsies. But in most cases, a radiologist (a doctor who specializes in x rays and imaging studies) performs the biopsy. The radiologist will use **computed tomography** scan (CT scan) or ultrasound to guide the choice of the site for the biopsy.

An hour or so before the biopsy, the patient may be given a sedative to help relaxation. He or she is then asked to lie on the back with the right elbow to the side and the right hand under the head. The patient is instructed to lie as still as possible during the procedure. He or she is warned to expect a sensation resembling a punch in the right shoulder, but to hold still in spite of the momentary feeling.

The doctor marks a spot on the skin where the needle will be inserted and thoroughly cleanses the right side of the upper abdomen with an antiseptic solution. The patient is then given an anesthetic at the biopsy site.

The needle with attached syringe is inserted into the patient's chest wall. The doctor then draws the plunger of the syringe back to create a vacuum. At this point the patient is asked to take a deep breath, exhale the air and hold their breath at the point of complete exhalation. The needle is inserted into the liver and withdrawn quickly, usually within two seconds or less. The negative pressure in the syringe draws or pulls a sample of liver tissue into the biopsy needle. As soon as the needle is withdrawn, the patient can breathe normally. Pressure is applied at the biopsy site to stop any bleeding, and a bandage will be placed over it. The entire procedure takes 10 to 15 minutes. Test results are usually available within a day.

Preparation

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are known to thin the blood and interfere with clotting. These medications should be avoided for at least a week before the biopsy. Four to eight hours before the biopsy, patients should stop eating and drinking.

The patient's blood will be tested prior to the biopsy to make sure that it is clotting normally. Tests will include a platelet count and a prothrombin time. Doctors will also ensure that the patient is not taking any other medications, such as blood thinners like Coumadin, that might affect blood clotting.

Aftercare

Liver biopsies are outpatient procedures in most hospitals. After the biopsy, patients are usually instructed to lie on their right side for about two hours. This provides pressure to the biopsy site and helps prevent bleeding. A nurse will check the patient's vital signs at regular intervals. If there are no complications, the patient is sent home within about four to eight hours.

Patients should arrange to have a friend or relative take them home after discharge. Bed rest for a day is recommended, followed by a week of avoiding heavy work or strenuous exercise. The patient can resume eating a normal diet.

Some mild soreness in the area of the biopsy is normal after the anesthetic wears off. Irritation of the muscle

QUESTIONS TO ASK THE DOCTOR

- Which medications should I stop taking before the biopsy?
- How soon can I return to my normal activities after the biopsy?
- How soon will I get my results?

that lies over the liver can also cause mild discomfort in the shoulder for some patients. Tylenol can be taken for minor soreness, but aspirin and NSAIDs are best avoided. Patients should call their doctor if they have severe pain in the abdomen, chest or shoulder, difficulty breathing, or persistent bleeding. These signs may indicate that there has been leakage of bile into the abdominal cavity, or that air has been introduced into the cavity around the lungs.

Risks

The risks of a liver biopsy are usually very small. When complications do occur, over 90% are apparent within 24 hours after the biopsy. The most significant risk is internal bleeding. Bleeding is most likely to occur in elderly patients, in patients with cirrhosis, or in patients with a tumor that has many blood vessels. Other complications from percutaneous liver biopsies include the leakage of bile or the introduction of air into the chest cavity (pneumothorax). There is also a small chance that an infection may occur, or an internal organ such as the lung, gallbladder, or kidney could be punctured.

Normal results

After the biopsy, the liver sample is sent to the pathology laboratory for study under a microscope. A normal (negative) result would find no evidence of cancer or other disease in the tissue sample.

Abnormal results

Changes in liver tissue that are visible under the microscope indicate abnormal results. Possible causes for the abnormality include the presence of a tumor, or a disease such as hepatitis.

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Lata Cherath, Ph.D.

Liver cancer

Definition

Liver cancer is a relatively rare form of cancer but has a high mortality rate. Liver cancers can be classified into two types. They are either primary, when the cancer starts in the liver itself, or metastatic, when the cancer has spread to the liver from some other part of the body.

Description and demographics

Primary liver cancer

Primary liver cancer is a relatively rare disease in the United States, representing about 2% of all malignancies and 4% of newly diagnosed cancers. Hepatocellular **carcinoma** (HCC) is the fifth most common cancer in the world as of 2004. It is much more common outside the United States, representing 10% to 50% of malignancies in Africa and parts of Asia. Rates of HCC in men are at least two to three times higher than for women. In high–risk areas (East and Southeast Asia, sub-Saharan Africa), men are even more likely to have HCC than women.

According to the American Cancer Society, 18,920 people in the United States will be diagnosed with primary liver cancer in 2004, and 14,270 persons will die from the disease. The incidence of primary liver cancer has been rising in the United States and Canada since the mid-1990s, most likely as a result of the rising rate of hepatitis C infections.

TYPES OF PRIMARY LIVER CANCER In adults, most primary liver cancers belong to one of two types: hepatomas, or hepatocellular carcinomas (HCC), which start in the liver tissue itself; and cholangiomas, or cholangiocarcinomas, which are cancers that develop in the bile ducts inside the liver. About 80% to 90% of primary liver

cancers are hepatomas. In the United States, about five persons in every 200,000 will develop a hepatoma (70% to 75% of cases of primary liver cancers are HCC). In Africa and Asia, over 40 persons in 200,000 will develop this form of cancer (more than 90% of cases of primary liver are HCC). Two rare types of primary liver cancer are mixed-cell tumors and Kupffer cell **sarcomas**.

One type of primary liver cancer, called a hepatoblastoma, usually occurs in children younger than four years of age and between the ages of 12 and 15. Unlike liver cancers in adults, hepatoblastomas have a good chance of being treated successfully. Approximately 70% of children with hepatoblastomas experience complete cures. If the tumor is detected early, the survival rate is over 90%.

Metastatic liver cancer

The second major category of liver cancer, metastatic liver cancer, is about 20 times more common in the United States than primary liver cancer. Because blood from all parts of the body must pass through the liver for filtration, cancer cells from other organs and tissues easily reach the liver, where they can lodge and grow into secondary tumors. Primary cancers in the colon, stomach, pancreas, rectum, esophagus, breast, lung, or skin are the most likely to metastasize (spread) to the liver. It is not unusual for the metastatic cancer in the liver to be the first noticeable sign of a cancer that started in another organ. After cirrhosis, metastatic liver cancer is the most common cause of fatal liver disease.

Causes and symptoms

Risk factors

The exact cause of primary liver cancer is still unknown. In adults, however, certain factors are known to place some individuals at higher risk of developing liver cancer. These factors include:

- Male sex.
- Age over 60 years.
- Ethnicity. Asian Americans with cirrhosis have four times as great a chance of developing liver cancer as Caucasians with cirrhosis, and African Americans have twice the risk of Caucasians. In addition, Asians often develop liver cancer at much younger ages than either African Americans or Caucasians.
- Exposure to substances in the environment that tend to cause cancer (carcinogens). These include: a substance produced by a mold that grows on rice and peanuts (aflatoxin); thorium dioxide, which was once used as a contrast dye for x rays of the liver; vinyl chloride, used in manufacturing plastics; and cigarette smoking.
- Use of oral estrogens for birth control.
- Hereditary hemochromatosis. This is a disorder characterized by abnormally high levels of iron storage in the body. It often develops into cirrhosis.
- Cirrhosis. Hepatomas appear to be a frequent complication of cirrhosis of the liver. Between 30% and 70% of hepatoma patients also have cirrhosis. It is estimated that a patient with cirrhosis has 40 times the chance of developing a hepatoma than a person with a healthy liver.
- Exposure to hepatitis viruses: Hepatitis B (HBV), Hepatitis C (HCV), Hepatitis D (HDV), or Hepatitis G (HGV). It is estimated that 80% of worldwide HCC is associated with chronic HBV infection. In Africa and most of Asia, exposure to hepatitis B is an important factor; in Japan and some Western countries, exposure to hepatitis C is connected with a higher risk of developing liver cancer. In the United States, nearly 25% of patients with liver cancer show evidence of HBV infection. Hepatitis is commonly found among intravenous drug abusers. The increase in HCC incidence in the United States is thought to be due to increasing rates of HBV and HCV infections due to increased sexual promiscuity and illicit drug needle sharing. The association between HDV and HGV and HCC is unclear as of the early 2000s.

Symptoms of liver cancer

The early symptoms of primary, as well as metastatic, liver cancer are often vague and not unique to liver disorders. The long period between the beginning of the tumor's growth and the first signs of illness is the major reason why the disease has a high mortality rate. At the time of diagnosis, patients are often fatigued, with **fever**, abdominal pain, and loss of appetite (anorexia). They may look emaciated and generally ill. As the tumor enlarges, it stretches the membrane surrounding the liver (the capsule), causing pain in the upper abdomen on the right side. The pain may extend into the back and shoulder. Some patients develop a collection of fluid, known as **ascites**, in the abdominal cavity. Others may show signs of bleeding into the digestive tract. In addition, the tumor may block the ducts of the liver or the gall bladder, leading to jaundice. In patients with jaundice, the whites of the eyes and the skin may turn yellow, and the urine becomes dark–colored.

Diagnosis

Physical examination

If the doctor suspects a diagnosis of liver cancer, he or she will check the patient's history for risk factors and pay close attention to the condition of the patient's abdo-

men during the physical examination. Masses or lumps in the liver and ascites can often be felt while the patient is lying flat on the examination table. The liver is usually swollen and hard in patients with liver cancer; it may be sore when the doctor presses on it. In some cases, the patient's spleen is also enlarged. The doctor may be able to hear an abnormal sound (bruit) or rubbing noise (friction rub) if he or she uses a stethoscope to listen to the blood vessels that lie near the liver. The noises are caused by the pressure of the tumor on the blood vessels.

Laboratory tests

Blood tests may be used to test liver function or to evaluate risk factors in the patient's history. Between 50% and 75% of primary liver cancer patients have abnormally high blood serum levels of a particular protein (alpha-fetoprotein or AFP). The AFP test, however, cannot be used by itself to confirm a diagnosis of liver cancer, because cirrhosis or chronic hepatitis can also produce high alpha–fetoprotein levels. Tests for alkaline phosphatase, bilirubin, lactic dehydrogenase, and other chemicals indicate that the liver is not functioning normally. About 75% of patients with liver cancer show evidence of hepatitis infection. Again, however, abnormal liver function test results are not specific for liver cancer.

Imaging studies

Imaging studies are useful in locating specific areas of abnormal tissue in the liver. Liver tumors as small as an inch across can now be detected by ultrasound or **computed tomography** scan (CT scan). Imaging studies, however, cannot tell the difference between a hepatoma and other abnormal masses or lumps of tissue (nodules) in the liver. A sample of liver tissue for **biopsy** is needed to make the definitive diagnosis of a primary liver cancer. CT or ultrasound can be used to guide the doctor in selecting the best location for obtaining the biopsy sample.

Chest x rays may be used to see whether the liver tumor is primary or has metastasized from a primary tumor in the lungs.

Liver biopsy

Liver biopsy is considered to provide the definite diagnosis of liver cancer. A sample of the liver or tissue fluid is removed with a fine needle and is checked under a microscope for the presence of cancer cells. In about 70% of cases, the biopsy is positive for cancer. In most cases, there is little risk to the patient from the biopsy procedure. In about 0.4% of cases, however, the patient develops a fatal hemorrhage from the biopsy because some tumors are supplied with a large number of blood vessels and bleed very easily.

Laparoscopy

The doctor may also perform a **laparoscopy** to help in the diagnosis of liver cancer. First, the doctor makes a small cut in the patient's abdomen and inserts a small, lighted tube called a laparoscope to view the area. A small piece of liver tissue is removed and examined under a microscope for the presence of cancer cells.

Clinical staging

Currently, the pathogenesis of HCC is not well understood. It is not clear how the different risk factors for HCC affect each other. In addition, the environmental factors vary from region to region.

Treatment

Treatment of liver cancer is based on several factors, including the type of cancer (primary or metastatic); stage (early or advanced); the location of other primary cancers or metastases in the patient's body; the patient's age; and other coexisting diseases, including cirrhosis. For many patients, treatment of liver cancer is primarily intended to relieve the pain caused by the cancer but cannot cure it.

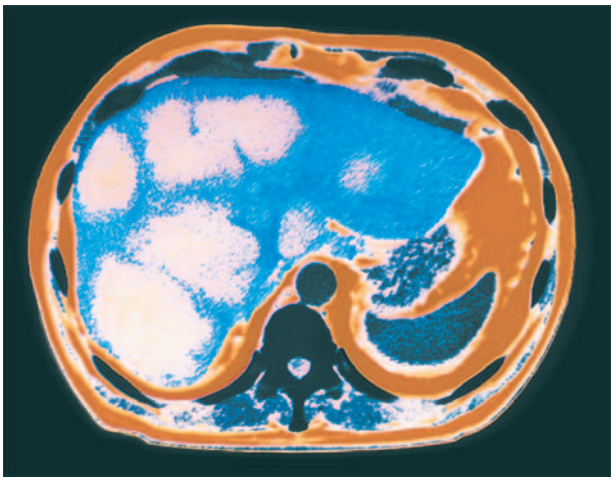
Surgery

Few liver cancers in adults can be cured by surgery because they are usually too advanced by the time they are discovered. If the cancer is contained within one lobe of the liver, and if the patient does not have either cirrhosis, jaundice, or ascites, surgery is the best treatment option. Patients who can have their entire tumor removed have the best chance for survival. Unfortunately, only about 5% of patients with metastatic cancer (from primary tumors in the colon or rectum) fall into this group. If the entire visible tumor can be removed, about 25% of patients will be cured. The operation that is performed is called a partial hepatectomy, or partial removal of the liver. The surgeon will remove either an entire lobe of the liver (a **lobectomy**) or cut out the area around the tumor (a wedge resection).

A newer technique that is reported to be safe and effective is laparoscopic radiofrequency ablation (RFA). RFA is a technique in which the surgeon places a special needle electrode in the tumor under guidance from MRI or CT scanning. When the electrode has been properly placed, a radiofrequency current is passed through it, heating the tumor and killing the cancer cells. RFA can be used to treat tumors that are too small or too inaccessible for removal by conventional open surgery.

Chemotherapy

Some patients with metastatic cancer of the liver can have their lives prolonged for a few months by



Colored computed tomography (CT) scan of axial section through the abdomen showing liver cancer. The vertebra appears dark blue, the liver is large and appears light blue, and the light patches on the liver are the cancerous tumors. *(Copyright Department of Clinical Radiology, Salisbury District Hospital, Science Source/Photo Researchers, Inc. Photo reproduced by permission.)*

chemotherapy, although cure is not possible. If the tumor cannot be removed by surgery, a tube (catheter) can be placed in the main artery of the liver and an implantable infusion pump can be installed. The pump allows much higher concentrations of the cancer drug to be carried to the tumor than is possible with chemotherapy carried through the bloodstream. The drug that is used for infusion pump therapy is usually **floxuridine** (FUDR), given for 14-day periods alternating with 14-day rests. Systemic chemotherapy can also be used to treat liver cancer. The medications usually used are 5-fluorouracil (Adrucil, Efudex) or **methotrexate** (MTX, Mexate). Systemic chemotherapy does not, however, significantly lengthen the patient's survival time.

Radiation therapy

Radiation therapy is the use of high-energy rays or x-rays to kill cancer cells or to shrink tumors. Its use in liver cancer, however, is only to give short-term relief from some of the symptoms. Liver cancers are not sensitive to radiation, and radiation therapy will not prolong the patient's life.

Liver transplantation

Removal of the entire liver (total hepatectomy) and liver transplantation can be used to treat liver cancer. However, there is a high risk of tumor recurrence and metastases after transplantation. In addition, most patients have cancer that is too far advanced at the time of diagnosis to benefit from liver transplantation.

Other therapies

Other therapeutic approaches include:

- Hepatic artery embolization with chemotherapy (chemoembolization).
- Alcohol ablation via ultrasound-guided percutaneous injection.
- Ultrasound-guided cryoablation.
- Immunotherapy with **monoclonal antibodies** tagged with cytotoxic agents.
- Gene therapy with retroviral vectors containing genes expressing cytotoxic agents.

Alternative and complementary therapies

Many patients find that alternative and complementary therapies help to reduce the stress associated with illness, improve immune function, and boost spirits. While there is no clinical evidence that these therapies specifically combat disease, such activities as biofeedback, relaxation, therapeutic touch, massage therapy and guided imagery have no side effects and have been reported to enhance well-being.

Several other healing therapies are sometimes used as supplemental or replacement cancer treatments, such as antineoplastons, cancell, cartilage (bovine and shark), laetrile, and mistletoe. Many of these therapies have not been the subject of safety and efficacy trials by the National Cancer Institute (NCI). The NCI has conducted trials on cancell, laetrile, and some other alternative therapies and found no anticancer activity. These treatments have varying effectiveness and safety considerations. (Laetrile, for example, has caused deaths and is not available in the U.S.) Patients using any alternative remedy should first consult their doctors in order to prevent harmful side effects or interactions with traditional cancer treatment.

Prognosis

Liver cancer has a very poor prognosis because it is often not diagnosed until it has metastasized. Fewer than 10% of patients survive three years after the initial diagnosis; the overall five-year survival rate for patients with hepatomas is around 4%. Most patients with primary liver cancer die within six months of diagnosis, usually from liver failure; fewer than 5% are cured of the disease. Patients with liver cancers that metastasized from cancers in the colon live slightly longer than those whose cancers spread from cancers in the stomach or pancreas.

As of 2004, African American and Hispanic patients have much lower 5-year survival rates than Caucasian patients. It is not yet known, however, whether cultural

KEY TERMS

Aflatoxin—A substance produced by molds that grow on rice and peanuts. Exposure to aflatoxin is thought to explain the high rates of primary liver cancer in Africa and parts of Asia.

Alpha-fetoprotein—A protein in blood serum that is found in abnormally high concentrations in most patients with primary liver cancer.

Cirrhosis—A chronic degenerative disease of the liver, in which normal cells are replaced by fibrous tissue. Cirrhosis is a major risk factor for the later development of liver cancer.

Cryoablation—A technique for removing cancerous tissue by killing it with extreme cold.

Hepatitis—A viral disease characterized by inflammation of the liver cells (hepatocytes). People infected with hepatitis B or hepatitis C virus are at an increased risk for developing liver cancer.

Metastatic cancer—A cancer that has spread to an organ or tissue from a primary cancer located elsewhere in the body.

Radiofrequency ablation—A technique for removing a tumor by heating it with a radiofrequency current passed through a needle electrode.

differences as well as biological factors may be partly responsible for the variation in survival rates.

Coping with cancer treatment

Side effects of treatment, nutrition, emotional well-being, and other issues are all parts of coping with cancer. There are many possible side effects for a cancer treatment that include:

- constipation
- delirium
- fatigue
- fever, chills, sweats
- nausea and vomiting
- mouth sores, dry mouth, bleeding gums
- pruritus (itching)
- affected **sexuality**
- sleep disorders

Anxiety, **depression**, feelings of loss, post-traumatic stress disorder, affected sexuality, and substance abuse are all possible emotional side-effects. Patients should seek out a support network to help them through treatment. Loss of appetite before, during, and after a treatment can also be of concern. Other complications of coping with cancer treatment include fever and pain.

Clinical trials

As of 2004, the National Cancer Institute is sponsoring 55 **clinical trials** of treatments for primary liver cancer in adults and 13 trials for treatments of primary liver cancer in children. These trials allow researchers to investigate new types of radiation therapy and chemotherapy, new drugs and drug combinations, biological therapies, ways of combining various types of treatment for liver cancer, side effect reduction, and quality of life. Information on clinical trials can be acquired from the National Cancer Institute at <http://www.nci.nih.gov> or (800) 4-CANCER.

Prevention

There are no useful strategies at present for preventing metastatic cancers of the liver. Primary liver cancers, however, are 75% to 80% preventable. Current strategies focus on widespread vaccination for hepatitis B, early treatment of hereditary hemochromatosis (a metabolic disorder), and screening of high-risk patients with alpha-fetoprotein testing and ultrasound examinations.

Lifestyle factors that can be modified in order to prevent liver cancer include avoidance of exposure to toxic chemicals and foods harboring molds that produce aflatoxin. Most important, however, is avoidance of alcohol and drug abuse. Alcohol abuse is responsible for 60–75% of cases of cirrhosis, which is a major risk factor for eventual development of primary liver cancer. Hepatitis is a widespread disease among persons who abuse intravenous drugs.

See also Alcohol consumption; CT-guided biopsy; Hepatic arterial infusion; Immunologic therapy.

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QUESTIONS TO ASK THE DOCTOR

- What type of liver cancer do I have?
- What is the stage of the disease?
- What are the treatment choices? Which do you recommend? Why?
- What are the risks and possible side effects of each treatment?
- What are the chances that the treatment will be successful?
- What new treatments are being studied in clinical trials?
- How long will treatment last?
- Will I have to stay in the hospital?
- Will treatment affect my normal activities? If so, for how long?
- What is the treatment likely to cost?

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) 227-2345. <http://www.cancer.org>.

American Institute for Cancer Research (AICR). 1759 R St. NW, Washington, DC 20009. (800) 843-8114. <http://www.aicr.org>.

American Liver Foundation. 908 Pompton Ave., Cedar Grove, NJ 07009. (800) 223-0179.

Cancer Care, Inc. 275 Seventh Ave., New York, NY 10001.(800) 813-HOPE. <http://www.cancercare.org>.

Cancer Hope Network. Suite A., Two North Rd., Chester, NJ 07930. (877) HOPENET. <http://www.cancerhopenetwork.org>.

Hospicelink. Hospice Education Institute, 190 Westbrook Rd., Essex, CT, 06426-1510. (800) 331-1620. <http://www.hospiceworld.com>.

National Cancer Institute (National Institutes of Health). 9000 Rockville Pike, Bethesda, MD 20892. (800) 422-6237. <http://www.nci.nih.gov>.

The Wellness Community. Suite 412, 35 E. Seventh St., Cincinnati, OH 45202. (888) 793-9355. <http://www.wellness-community.org>.

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Rebecca J. Frey, Ph.D.
Laura Ruth, Ph.D.

Liver cancer, secondary *see* **Metastasis**

Liver scan *see* **Nuclear medicine scans**

Lobectomy

Definition

A lobectomy is the removal of a lobe of one of the organs, usually referring to the brain, the lung, or the liver.

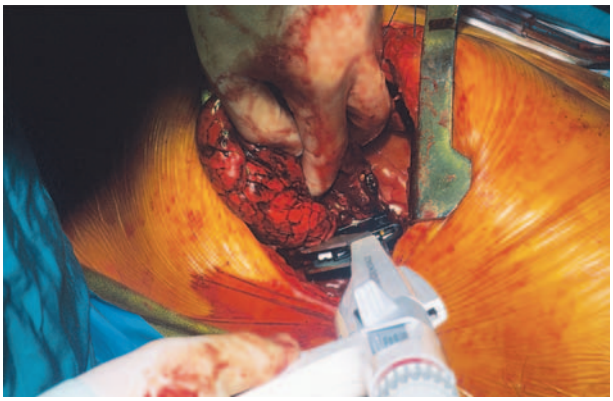
Purpose

Lobectomies are usually performed to prevent the spread of cancer from one part of an organ to other parts or to other parts of the body. Lobectomies also are performed on patients with severe seizure disorders (such as some forms of epilepsy) to prevent further seizures. However, there are differences in each of the three organs on which lobectomies may be performed.

Description

The brain

Each lobe of the brain performs a different function, and when part of the brain is removed, it does not grow back. However, other parts of the brain can take over some, or all, of the function of the missing part of the brain. Depending on the part of the brain removed, the effects may be quite severe, or nearly nonexistent.



Left upper lobectomy. A surgeon is using a stapling device to ligate (tie or bind) the left upper bronchus. The lobar veins and arteries have already been ligated. *(Custom Medical Stock Photo. Reproduced by permission.)*

The most commonly referenced brain lobectomy in the medical literature is the removal of the temporal lobe. Temporal lobectomy usually is performed to prevent debilitating seizures. Seizures are commonly caused by temporal lobe epilepsy, but can also be caused by brain tumors in the temporal lobe. Thus, lobectomy of the temporal lobe in patients with a temporal lobe tumor reduces or eliminates seizures, and has the beneficial side effect of removing the tumor mass.

The lung

Lobectomies of the lung also are called pulmonary lobectomies. Each part of the lung performs the same function: it exchanges oxygen for carbon dioxide in the blood. There are many different lobes of the lung, however, and some lobes exchange more oxygen than others. Lobes of the lung do not regenerate after they are removed. Therefore, removal of a large portion of the lung may cause a person to need oxygen or ventilator support for the rest of his or her life. However, removal of a small portion of the lung may result in very little change to the patient's quality of life. A test (a quantitative ventilation/perfusion scan, or quantitative V/Q scan) may be used before surgery to help determine how much of the lung can safely be removed.

The outcome of lung lobectomies also depends on the general health of the entire lung; emphysema and smoking would have a negative impact on the health of a patient's lung. The surgeon may perform the surgery with video assistance and special tools to decrease pain and speed patient recovery following surgery.

The liver

A lobectomy of the liver is also called a hepatic lobectomy. The liver plays a major role in digestion, in the transformation of food into energy, and in filtering and storing blood. It processes nutrients and drugs, produces bile, controls the level of glucose (sugar) in the blood, detoxifies blood, and regulates blood clotting. Unlike the brain and the lung, the liver may regrow, or regenerate, after part of the liver has been removed. In addition, since every part of the liver performs the same functions, the liver is the organ whose function is least likely to be severely affected by lobectomy, in the long term, because it regenerates. However, as the liver is central to the body's functions, removal of too much of the liver at once may result in coma or death.

Precautions

Brain lobectomies should not be performed unless the patient has been unable to control seizures through medication. Additionally, the seizures must be caused by a single, relatively small, localized part of the brain that can be resected without severe damage. Lung lobectomies should only be performed on patients with early stage non-small cell **carcinoma** of the lung, or as part of a combination of therapies at later stages. Since even a "complete removal" of the tumor does not result in an overwhelming survival rate after five years, other therapies also may be considered. Small cell cancer of the lung does not respond to surgical intervention. Patients with liver disease that is too extensive may need a liver transplant rather than a liver lobectomy. Patients with blood clotting problems, either due to chemotherapeutic agents or for other reasons, should have these problems addressed before surgery.

Preparation

Before surgery, patients should not take aspirin or ibuprofen for one week. Patients also should consult their physician about any blood-thinning medications such as coumadin or **warfarin**. The night before surgery, patients will usually be asked not to eat or drink after a certain time.

Aftercare

Each surgery offers different aftercare challenges. Patients may need to be hospitalized for some time after the operation. Patients with portions of their brain removed may require rehabilitation of a physical, mental, or emotional nature depending on the portion of the brain that has been removed. Patients who have had portions of their lungs removed probably will require a tube in their chest to drain fluid, and may require a machine to help them breathe. They also may require oxygen, either on a temporary or permanent basis. Patients who have had hepatic lobectomies also may have drainage tubes, and may also have initial dietary restrictions. Physicians

QUESTIONS TO ASK THE DOCTOR

- What benefits can I expect from this operation?
- What are the risks of this operation?
- What are the normal results of this operation?
- What happens if this operation doesn't go as planned?
- What is the expected recovery time?

should be consulted for the specifics of aftercare in each individual situation.

Risks

Specific risks vary from surgery to surgery and should be discussed with a physician. In general, any surgery requiring a general anesthetic may, uncommonly, result in death. Improperly performed brain surgery may result in permanent brain damage. Depending on the surgeon and the size of the tissue removed, patients may be at risk for some types of brain damage. As previously mentioned, patients having part of a lung removed may have difficulty breathing and may require the use of oxygen. Patients also may experience infection (**pneumonia**), or blood clots. Liver resection (surgery) may result in the following complications: coma, slow return of normal bowel function, and biliary leakage.

Normal results

Most patients who undergo temporal lobectomy experience few or no seizures after surgery (some estimates range from about 70% to about 90% success rate). Unfortunately, lung lobectomy is not as successful. 50% of cancer patients with completely removable stage I non-small cell cancer of the lung survive five years after the procedure. If the cancer has progressed beyond this stage, or if the cancer is not completely removable, the chances for survival drop significantly. The results of liver resection vary. The possible outcomes of each surgical type should be discussed with the patient's physician. Generally, the less severe the cancer, and the less tissue that needs to be removed, the better the outcome.

Abnormal results

Abnormal results vary from operation to operation and should be discussed thoroughly with the patient's physician before surgery. Patients who undergo temporal lobectomy may, rarely, die as a result of the operation (a complication in less than 1% of patients). Patients also may have problems with their vision, or problems with speech. Abnormal results from the removal of part of the lung could include pneumonia or blood clots (which may result in stroke, heart attack, or other problems) after the surgery. Also, a small percentage of patients undergoing lung lobectomy die during or soon after the surgery. The percentage of patients who suffer death varies from about 3% to 6% depending on the amount of lung tissue removed. Finally, abnormal outcomes from liver resection can include coma, death, and problems with liver function.

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Michael Zuck, Ph.D.
Teresa G. Odle

Lomustine

Definition

Lomustine is one of the anticancer (antineoplastic) drugs in a class called alkylating agents. It is available under the brand name CeeNU. Another commonly used name is CCNU.

Purpose

Lomustine is primarily used to treat brain tumors and **Hodgkin's disease**, which is a type of cancer that affects the lymph nodes and spleen.

Description

Lomustine chemically interferes with the synthesis of genetic material (DNA and RNA) of cancer cells, which prevents these cells from being able to reproduce and continue the growth of the cancer.

Recommended dosage

Lomustine is taken orally (in pill form). The dosage is typically 100 to 130 mg per square meter of body surface area once every 6 weeks. Lomustine should be taken on an empty stomach just prior to bedtime to prevent possible nausea and/or vomiting. Patients should avoid alcohol one hour before and shortly after taking lomustine.

Precautions

Lomustine can cause an allergic reaction in some people. Patients with a prior allergic reaction to lomustine should not take this drug.

Lomustine can cause harm to the fetus if a woman is taking this drug during pregnancy. Women of childbearing potential should use appropriate contraceptive measures to prevent pregnancy while on lomustine. There have been reports of infertility in men taking this drug due to testicular damage.

It is not known if lomustine is excreted in breast milk. Because of the potential of severe adverse effect, it is recommended that breastfeeding women should discuss with their physician the risk versus benefit of breastfeeding while taking lomustine.

Side effects

Common side effects of lomustine include nausea and/or vomiting, as well as an increased susceptibility to infection due to decreased production in the cells that fight infections. Patients should avoid crowds or exposure to any individuals who may have infections. Also, an increased risk of bleeding can occur due to decreased production of the platelets that are involved with the blood clotting process.

Less common side effects that may also occur include loss of appetite (anorexia), **diarrhea**, temporary hair loss (alopecia), and skin rash.

A doctor should be consulted immediately if the patient experiences any of the following effects:

- black, tarry or bloody stools
- blood in the urine
- confusion
- persistent cough

KEY TERMS

Antineoplastic—A drug that prevents the growth of a neoplasm by interfering with the maturation or proliferation of the cells of the neoplasm.

Neoplasm—New abnormal growth of tissue.

Hodgkins disease—A disease characterized by enlargement of the lymph nodes and spleen.

- fever and chills
- sore throat
- red spots on the skin
- shortness of breath
- unusual bleeding or bruising

Interactions

Lomustine should not be taken in combination with any prescription drug, over-the-counter drug, or herbal remedy without prior consultation with a physician.

Paul A. Johnson, Ed.M.

Loperamide *see* **Antidiarrheal agents**

Lorazepam

Definition

Lorazepam is a tranquilizing drug used in managing anxiety, **nausea and vomiting**, insomnia, and seizures.

Purpose

Lorazepam decreases anxiety. Doctors may order it to treat muscle spasms that may accompany severe pain. Lorazepam may also be given with other drugs to help control nausea and vomiting associated with cancer treatment. It may be given just prior to the administration of **chemotherapy** to decrease the chances of nausea and vomiting. Patients experiencing difficulty sleeping may receive lorazepam. It is sometimes given prior to surgery or other procedures to help the patient relax, feel drowsy, and decrease his or her memory about the procedure.

Description

Lorazepam depresses the central nervous system when taken at the recommended dose.

Recommended dosage

Lorazepam may be given by mouth, injected into a muscle or administered through a vein. Patients should take the smallest dose possible that relieves symptoms. The dose should be adjusted based on the patient's reaction to the drug. Between 0.5 mg and 1 mg of Lorazepam may be given every six to eight hours to aid in controlling treatment-related nausea and vomiting. When given prior to chemotherapy to decrease the risk of this side effect, 2 mg is usually administered 30 minutes before treatment. An additional 2 mg may be given every four hours as needed. To control anxiety, 1 mg to 3 mg at two to three times per day is the typical dose. For sleep, patients may take from 2 mg to 4 mg at bedtime. Older or debilitated adults may be given 0.5 mg to 2 mg per day in divided doses. If a dose is missed, the patient should take it as soon as possible, but patients should not take two pills at the same time. This drug may be taken with or without food.

In 2004, a company called Intranasal Technology, Ltd. received a patent to develop a nasal form of lorazepam. By delivering the drug through the nose (nasal passages), its developers showed it could work faster with fewer side effects. Intranasal Technology was developing a small, inexpensive, manually operated, disposable device to administer the lorazepam.

Precautions

Lorazepam, like other drugs of this type, can create physical and mental dependence. Patients should not take more than the amount ordered and should not suddenly stop taking this medication. The amount taken should gradually be decreased, then discontinued. If the drug is abruptly stopped, the patient may experience agitation, irritability, difficulty sleeping, convulsions, and other withdrawal symptoms.

Patients allergic to this type of anti-anxiety drug should not take lorazepam. Those with narrow-angle glaucoma, pre-existing **depression** of the central nervous system, severe uncontrolled pain, or severe decrease in blood pressure should avoid taking it. This drug should be used cautiously in patients with kidney or liver disease, **myasthenia gravis**, lung disease, alcohol intoxication, or anyone with a history of drug abuse. This drug should not be given to children under 12. Children between 12 and 18 may receive the drug by mouth, but not through a vein. Pregnant women and those trying to become pregnant should not take lorazepam. This drug has been associated with fetal malformations when taken during the first three months of pregnancy. Patients taking this drug should not breast feed their infants.

KEY TERMS

Hallucinations—Seeing or hearing things that are not present.

Tranquilizer—In pharmacology, a drug that calms and relieves anxiety.

Side effects

Drowsiness and sleepiness are common and expected effects of lorazepam. Patients should not drive or operate machinery or appliances while taking this drug. Patients older than 50 years of age may experience greater and longer sedation after receiving lorazepam. These effects may subside with continued use or if the dose is reduced. Patients may experience difficulty walking or fall easily for up to eight hours after receiving an injection of lorazepam, and should ask for assistance when walking. The effects of an injection may impair performance and driving ability for 24 to 48 hours. The impairments may last longer in older patients and those taking other central nervous system depressants, such as pain medication.

Lorazepam may also make patients feel dizzy, weak, unsteady, or clumsy. Less frequently, they may also feel depressed, disoriented, nauseous, or agitated while taking this drug. Other side effects include headache, difficulty sleeping, rash, yellowing eyes, vision changes, and hallucinations. Redness and pain may occur at the injection site. Patients may experience high or low blood pressure and partial blockage of the airway after an injection of lorazepam. Nausea, vomiting, dry mouth, and constipation may occur. Sex drive may decrease, but this side effect is reversible. Patients should alert their physician to any side effects of confusion, depression, excitation, depression, nightmares, impaired coordination, changes in personality, changes in urinary pattern, chest pain, heart palpitations, or any other side effects.

Interactions

Alcohol and other central nervous system depressants can increase the drowsiness associated with this drug. Some over-the-counter medications depress the central nervous system. The herbal remedies kava and valerian may increase the effects of this type of drug. Patients should check with the doctor before starting any new medication. A patient's tolerance for alcohol will be diminished. Patients should refrain from drinking alcoholic beverages when taking lorazepam and for 24 to 48 hours after receiving an injection before a procedure.

When lorazepam is administered in a muscle or vein, it may interact with **scopolamine**, causing drowsiness, odd behavior, and hallucinations.

Resources

PERIODICALS

"Company Announces Newly Patented Lorazepam Nasal Delivery System." *Drug Week* January 16, 2004: 223.

Debra Wood, R.N.
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Loss of appetite *see* **Anorexia**

Low molecular weight heparins

Definition

Low molecular weight heparins (LMWHs) belong to a class of medications known as blood thinners. They are used to stop blood clots from forming and growing.

Purpose

LMWHs are used to prevent and treat blood clots in persons undergoing certain types of surgery, recent heart attack, severe chest pain caused by disease of heart vessels usually from fat deposits (unstable angina), and people who have blood clots in their veins (also known as deep vein thrombosis or DVT) or lungs (also known as pulmonary embolism or PE). As of 2001, there are three drugs that belong to the class of LMWHs: enoxaparin, dalteparin, and tinzaparin. All three have the same mechanism of action, but differ in their doses, structures, and Food and Drug Administration (FDA) indicated uses.

Many cancer patients can become prone to hypercoagulation, or overactive thickening and clotting of the blood. This makes the patient more likely to experience deep vein thrombosis, possibly leading to death.

Description

LMWHs only became available in the mid-1990s, with enoxaparin (Lovenox) being the first and most studied drug in its class. Dalteparin (Fragmin) was the second LMWH to become available and tinzaparin (Innohep) is the latest addition to this class. These medicines work by inhibiting certain clotting factors in the blood (Factor Xa and thrombin) and preventing blood clots from forming and getting bigger.

LMWHs are closely related to **heparin**, which is one of the oldest blood thinners available. These drugs have an advantage over heparin in that they have longer duration in the body, more predictable effects after a given dose, require less blood tests to check for their effectiveness and side effects, and do not have to be given in the hospital setting only. LMWHs have been found to be safe and effective in blood clot prevention after general surgery, orthopedic surgery, neurosurgery, multiple trauma, hip fracture, certain types of stroke, unstable angina, heart attack and treatment DVT and PE. These drugs are usually given with **warfarin** (Coumadin) for treatment of blood clots and with aspirin for prevention of complications after heart attack or angina attack. Besides their use for blood clot prevention and treatment, there have been some research studies in animals and humans to suggest that they may prevent cancer by decreasing the blood supply needed for the tumor to grow. The effects of LMWHs on patients with cancer and blood clots are being investigated. In 2004, clinical trails suggested that LMWHs might interfere with tumor growth and cancer spread, but further study was needed.

Recommended dosage

Administration

These medicines are given by injection beneath the skin (subcutaneous injection) and should not be injected directly into the vein or muscle. Injections can be given around the navel, upper thigh or buttock. The injection site should be changed daily. Massaging of the site before injection with an ice cube can decrease excessive bruising.

Doses and indications differ between three medicines. These drugs can not be used interchangeably for one another.

Adults

PREVENTION OF BLOOD CLOTS AFTER ORTHOPEDIC SURGERY The usual dose of tinzaparin is 50 units per kg daily starting two hours before surgery and continuing for 7–10 days. Doses of 75 units per kg per day have also been studied.

PREVENTION OF BLOOD CLOTS AFTER HIP OR KNEE REPLACEMENT SURGERY Doses vary between different agents. The usual enoxaparin dose is 30 mg every 12 hours starting 12–24 hours after surgery in patients undergoing hip or knee surgery. Alternatively, 40 mg once a day with the first dose given approximately 12 hours before surgery can be used in patients undergoing hip replacement surgery. The average duration of the initial phase of treatment is 7–10 days (up to 14 days). After the initial phase, 40 mg once a day for three weeks is recommended.

For people undergoing hip replacement surgery, 5,000 units of dalteparin are given 10–14 hours before surgery, then 5,000 units 4–8 hours after surgery, followed by 5,000 units daily. The therapy is usually continued for five to ten days (up to 14 days). A physician should be consulted for alternative dosing regimens.

PREVENTION OF DVT IN PATIENTS AT HIGH RISK FOR BLOOD CLOTS AFTER ABDOMINAL SURGERY. Enoxaparin is usually given at a dose of 40 mg once daily with the first dose given two hours before surgery for seven to ten days, up to 12 days.

In patients who are at moderate to high risk of blood clots, the usual dose of dalteparin is 2,500 units daily generally given for five to ten days. The first dose should be given one to two hours before surgery. In patients who are at high to very high risk of blood clots (those with cancer or history of DVT or PE) 5,000 units are given on the evening before surgery, followed by 5,000 units/day for five to ten days. A physician should be consulted for alternative dosing schedules.

Tinzaparin is usually dosed at 3,500 units daily starting two hours before surgery and continuing for seven to ten days.

TREATMENT OF DVT WITH OR WITHOUT PE Enoxaparin doses of 1 mg per kg twice a day are given when people are treated at home. People who are treated in the hospital can be given 1 mg per kg twice a day or 1.5 mg per kg at the same time once a day. Warfarin is usually given to finish treatment and the two drugs overlap for about 72 hours until good response to warfarin is confirmed by blood tests.

Tinzaparin is usually dosed at 175 units per kg daily for six days or until good response to warfarin is confirmed by blood tests.

UNSTABLE ANGINA OR HEART ATTACK In patients who are also getting aspirin the usual dose of enoxaparin is 1 mg per kg every 12 hours for a minimum of two days (usually two to eight days).

The usual dose of dalteparin in people who are also getting aspirin is 120 units per kg (up to a maximum 10,000 units) every 12 hours. Treatment should continue until the patient is stable for five to eight days.

Children

TREATMENT OF DVT WITH OR WITHOUT PE Children younger than two months of age should receive enoxaparin 1.5 mg per kg every 12 hours. Children older than two months of age should receive enoxaparin 1 mg per kg every 12 hours. A physician will do a blood test four to six hours after the dose to check for effectiveness.

PREVENTION OF BLOOD CLOTS The usual dose of enoxaparin is 0.75 mg per kg every 12 hours for children younger than two months and 0.5 mg per kg every 12 hours for children older than two months of age. A physician will do a blood test four to six hours after the dose to check for effectiveness.

Precautions

The use of LMWHs should be avoided in persons undergoing any procedure involving spinal puncture or anesthesia. Using these medicines before these procedures has caused severe bruising and bleeding into the spine and can lead to paralysis.

The use of these medicines should be avoided in patients with allergies to LMWHs, heparin, or pork products, allergies to sulfites or benzyl alcohol, people with active major bleeding, and people with a history of heparin-induced low blood platelet count (also known as heparin-induced **thrombocytopenia** or HIT).

LMWHs should be used with caution in the following persons:

- people with bleeding disorders
- people with a history of recent stomach ulcers
- people who recently had brain, spine, or eye surgery
- people on other blood thinners (such as warfarin, aspirin, ibuprofen, naproxen) because of increased risk of bleeding
- people with kidney or liver disease (the dose of LMWHs may need to be decreased)
- breast-feeding mothers (it is not known if these medicines cross into breast milk)
- women who are pregnant, unless benefits to the mother outweigh the risks to the baby

A doctor should be contacted immediately if any of these symptoms develop:

- tingling, weakness, numbness or pain
- blood in the urine or stool
- itching, swelling, skin rash, trouble breathing
- unusual bleeding or bruising

A physician may perform blood tests during therapy with LMWHs to prevent side effects. Blood tests to check for effectiveness of these medicines are usually not needed, except in children, people with kidney disease, and overweight persons.

Side effects

The most common side effects of LMWHs include irritation and pain at the injection site, easy bruising and

KEY TERMS

Deep vein thrombosis—Also known as DVT, a condition in which a blood clot (thrombus) formed in one part of the circulation, becomes detached and lodges at another point (usually in one of the veins of the legs or arms). People may feel pain, redness, and swelling at the site where the blood clot lodges in. This condition is treated with blood thinning drugs such as LMWHs, heparin, or warfarin.

Pulmonary embolism—Also known as PE, a condition in which a blood clot usually formed in of the leg veins becomes detached and lodges in the lung artery or one of its branches. Patients may be coughing up blood and experience trouble breathing. This condition is treated with blood thinning drugs such as LMWHs, heparin, or warfarin.

bleeding, **fever**, increase in liver enzyme tests usually without symptoms, and allergic reactions. Severe painful erection sometimes requiring surgery has been reported with tinzaparin in some patients. LMWHs can lower platelet counts, which may necessitate discontinuation.

Interactions

LMWHs should be used with caution in people on other oral blood thinners (aspirin, non-steroidal anti-inflammatory drugs, warfarin, and ticlopidine) because of increased risk of bleeding. If using both drugs together is necessary, the patients must be closely monitored.

Resources

PERIODICALS

"Low-molecular Weight Heparins May Interfere With Tumor Growth and Metastasis." *Drug Week* (July 2, 2004): 269.

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Lumbar puncture

Definition

Lumbar puncture (LP) is the technique of using a needle to withdraw cerebrospinal fluid (CSF) from the spinal canal. CSF is the clear, watery liquid that protects the central nervous system from injury and cushions it from the surrounding bone structure. It contains a variety of substances, particularly glucose (sugar), protein, and white blood cells from the immune system.

Purpose

Lumbar puncture, or spinal tap, is used to diagnose some malignancies, such as certain types of brain cancer and leukemia, as well as other medical conditions that affect the central nervous system. It is sometimes used to assess patients with certain psychiatric symptoms and conditions.

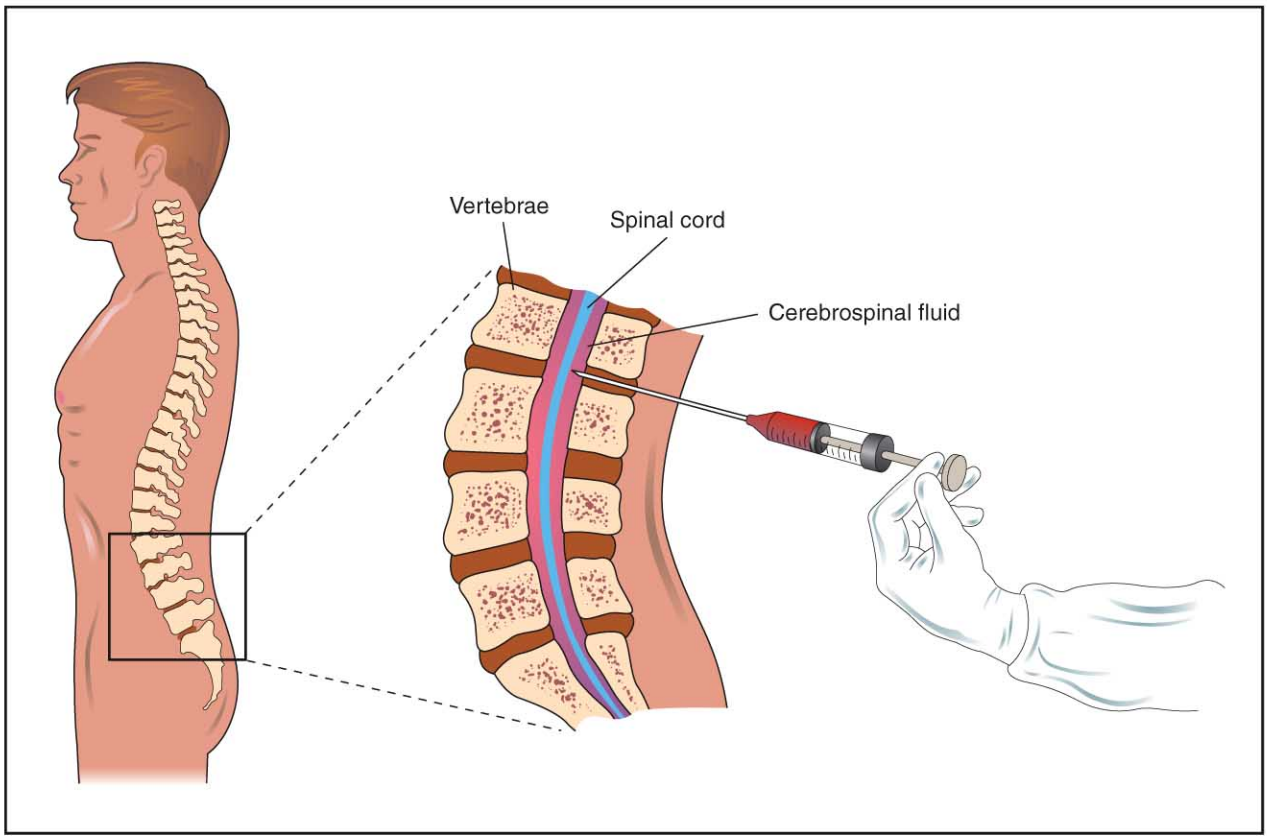
It is also used for injecting **chemotherapy** directly into the CSF. This type of treatment is called intrathecal therapy. Other medical conditions diagnosed with lumbar puncture include:

- viral and bacterial meningitis
- syphilis, a sexually transmitted disease
- bleeding (hemorrhaging) around the brain and spinal cord
- multiple sclerosis, a disease that affects the myelin coating of the nerve fibers of the brain and spinal cord
- Guillain-Barré syndrome, an inflammation of the nerves

Precautions

In some circumstances, a lumbar puncture to withdraw a small amount of CSF for analysis may lead to serious complications. Lumbar puncture should be performed only with extreme caution, and only if the benefits are thought to outweigh the risks, in certain conditions. For example, in people who have blood clotting (coagulation) or bleeding disorders or who are on anticoagulant treatment, lumbar puncture can cause bleeding that can compress the spinal cord. The term for this condition is spinal subdural hematoma, and it is a rare complication. However, it is of concern to some cancer patients whose low platelet counts (**thrombocytopenia**) make them more susceptible to bleeding. In some cases, these patients are given a platelet transfusion prior to lumbar puncture, but this procedure is still under investigation. A 1984–88 study, supported in part by the National Cancer Institute, researched the risk of lumbar puncture on children with acute lymphoblastic leukemia (ALL). No serious lumbar puncture complications were observed in this study of over 5,000 children.

Lumbar puncture has been shown to be less precise than some other methods in monitoring intracranial fluid pressure. A transducer provides more accurate information about changes in the flow of blood and cerebrospinal fluid within the brain.



During a lumbar puncture, or spinal tap, the physician inserts a hollow thin needle in the space between two vertebrae of the lower back and slowly advances it toward the spine. The cerebrospinal fluid pressure is then measured and some fluid is withdrawn for laboratory analysis. *(Electronic Illustrators Group.)*

A traumatic lumbar puncture (TLP) occurs when a blood vessel is inadvertently ruptured during the procedure. If this happens as part of a diagnostic leukemia workup, there is the potential of contaminating the CSF specimen that has been removed with leukemia cells, causing a false positive test result.

If there is a large brain tumor or other mass, removal of CSF can cause pressure shifts within the brain (herniation), causing compression of the brain stem and other vital structures, and leading to irreversible brain damage or death. These problems are easily avoided by checking blood coagulation through a blood test and by doing a **computed tomography** scan (CT) or **magnetic resonance imaging** (MRI) scan before attempting the lumbar puncture. In addition, a lumbar puncture procedure should never be performed at the site of a localized skin infection on the lower back because the infection may be introduced into the CSF and may spread to the brain or spinal cord.

Description

In a lumbar puncture, the area of the spinal column used to obtain the CSF sample is in the lumbar spine, or lower section of the back. In rare instances, such as a spinal fluid blockage in the middle of the back, a doctor may perform a spinal tap in the neck. The lower lumbar spine (usually between the vertebrae known as L4–5) is preferable because the spinal cord stops near L2, and a needle introduced below this level will miss the spinal cord and encounter only nerve roots, which are easily pushed aside.

A lumbar puncture takes about 15–30 minutes. Patients can undergo the test in a doctor's office, laboratory, or outpatient hospital setting. Sometimes it requires an inpatient hospital stay. If the patient has severe osteoarthritis of the spine, is extremely uncooperative, or obese, it may be necessary to introduce the spinal needle using x-ray guidance.

In order to get an accurate sample of cerebrospinal fluid, it is critical that a patient is in the proper position. The spine must be curved to allow as much space as possible between the lower vertebrae, or bones of the back, for the doctor to insert a lumbar puncture needle between the vertebrae and withdraw a small amount of fluid. The most common position is for the patient to lie on his or

KEY TERMS

Acute lymphoblastic leukemia (ALL)—A type of leukemia, also called acute lymphocytic leukemia, primarily in children, affecting lymphocytes.

Encephalitis—An inflammation or infection of the brain and spinal cord caused by a virus or as a complication of another infection.

Guillain-Barré syndrome—An inflammation involving nerves that affects the extremities. The inflammation may spread to the face, arms, and chest.

Immune system—Protects the body against infection.

Intrathecal therapy—Injecting chemotherapy directly into the CSF using lumbar puncture.

Manometer—A device used to measure fluid pressure.

Meningitis—An infection or inflammation of the membranes or tissues that cover the brain and spinal cord, and caused by bacteria or a virus.

Multiple sclerosis—A disease that destroys the covering (myelin sheath) of nerve fibers of the brain and spinal cord.

Spinal canal—The cavity or hollow space within the spine that contains cerebrospinal fluid.

Thrombocytopenia—Reduced platelet levels.

Vertebrae—The bones of the spinal column. There are 33 along the spine, with five (called L1–L5) making up the lower lumbar region.

her side with the back at the edge of the exam table, head and chin bent down, knees drawn up to the chest, and arms clasped around the knees. (Small infants and people who are obese may need to curve their spines in a sitting position.) People should talk to their doctors if they have any questions about their position because it is important to be comfortable and to remain still during the entire procedure. In fact, the doctor will explain the procedure to the patient (or guardian) so that the patient can agree in writing to have it done (informed consent). If the patient is anxious or uncooperative, a short-acting sedative may be given.

During a lumbar puncture, the doctor drapes the back with a sterile covering that has an opening over the puncture site and cleans the skin surface with an antiseptic solution. Patients receive a local anesthetic to minimize any pain in the lower back.

The doctor inserts a thin hollow needle in the space between two vertebrae of the lower back and slowly advances it through ligamentous tissues toward the spine. A steady flow of clear cerebrospinal fluid, normally the color of water, will begin to fill the needle as soon as it enters the spinal canal. The doctor measures the cerebrospinal fluid pressure with a special instrument called a manometer and withdraws several vials of fluid for laboratory analysis. The amount of fluid collected depends on the type and number of tests needed to diagnose a particular medical disorder.

In some cases, the doctor must remove and reposition the needle. This occurs when there is not an even flow of fluid, the needle hits bone or a blood vessel, or the patient reports sharp, unusual pain.

Preparation

Patients can go about their normal activities before a lumbar puncture. Experts recommend that patients relax before the procedure to release any muscle tension, since the lumbar puncture needle must pass through muscle tissue before it reaches the spinal canal. A patient's level of relaxation before and during the procedure plays a critical role in the test's success. Relaxation may be difficult for those patients who face frequent lumbar punctures, such as children with leukemia. In these cases, it is especially important for the child to receive psychological support before and after each procedure. It may be helpful to praise a child who remained still and quiet during the procedure, and to remind the child of his or her good behavior before the next lumbar puncture.

Aftercare

After the procedure, the doctor covers the site of the puncture with a sterile bandage. Patients must avoid sitting or standing and remain lying down for as long as six hours after the lumbar puncture. They should also drink plenty of fluids to help prevent lumbar puncture headache, which is discussed in the next section.

Risks

The most common side effect of lumbar puncture is a headache. This problem occurs in 10–20% of adult patients and in up to 40% of children. It is caused by decreased CSF pressure related to a small leak of CSF through the puncture site. These headaches usually are a dull pain, although some people report a throbbing sensation. A stiff neck and nausea may accompany the headache. A lumbar puncture headache typically begins within a few hours to two days after the procedure and usually persists a few days, although it can last several weeks or months.

QUESTIONS TO ASK THE DOCTOR

- What is the purpose of my lumbar puncture?
- What aftercare will be needed?
- Will lumbar puncture be used for chemotherapy, and if so, how often will I receive treatments?
- What are the risks for diagnostic procedures or treatments through lumbar puncture?
- What do the test results mean?
- What techniques are suggested to relax children before and after a lumbar puncture?

In some cases, the headache can be prevented by lying flat for an hour after the lumbar puncture, and taking in more fluids for 24 hours after the procedure. Since an upright position worsens the pain, lying flat also helps control the pain, along with prescription or non–prescription pain relief medication, preferably one containing caffeine. In rare cases, the puncture site leak is "patched" using the patient's own blood. People may also experience back pain. Headaches and backaches appear to be more common in adolescents than in younger children, and more common in girls than in boys.

Patients who receive anticancer drugs through lumbar puncture sometimes have **nausea and vomiting**. Intrathecal **methotrexate** can cause mouth sores. Some of these symptoms may be relieved by anti-nausea drugs prescribed by the physician.

In a very few cases, lumbar puncture in infants can lead to such complications as paraplegia. These complications are associated with the smaller size of the infant's central nervous system and increased difficulty in avoiding certain parts of the spinal cord when performing an LP.

People should talk to their doctors about complications from a lumbar puncture. In most cases, this procedure is safe and effective. Some patients experience pain, difficulty urinating, infection, or leakage of cerebrospinal fluid from the puncture site after the procedure.

Normal results

Normal CSF is clear and colorless. It may be straw or yellow–colored if there is excess protein, which may occur with cancer or inflammation. It may be cloudy in infections; blood–tinged if there was recent bleeding; or yellow to brown (xanthochromic) if caused by an older instance of bleeding.

A series of laboratory tests analyze the CSF for a variety of substances to rule out cancer or other medical disorders of the central nervous system. The following are normal values for commonly tested substances:

- CSF pressure: 50–180 mmH_2O
- Glucose: 40–85 mg/dL
- Protein: 15–50 mg/dL
- Leukocytes (white blood cells) total less than 5 per mL
- Lymphocytes (specific type of white blood cell): 60–70%
- Monocytes (a kind of white blood cell): 30–50%
- Neutrophils (another kind of white blood cell): none

Normally, there are no red blood cells in the CSF unless the needle passes though a blood vessel on route to the CSF. If this is the case, there should be more red blood cells in the first tube collected than in the last.

Abnormal results

A lumbar puncture is sometimes used as part of a diagnostic cancer workup. Abnormal test result values in the pressure or any of the substances found in the cerebrospinal fluid may suggest a number of medical problems including a tumor or spinal cord obstruction; hemorrhaging or bleeding in the central nervous system; infection from bacterial, viral, or fungal microorganisms; or an inflammation of the nerves. If there is a tumor in the meninges (membranes around the brain and spinal cord), the CSF may have higher protein levels, lower glucose levels, and a mild increase in lymphocytes (pleocytosis). It is important for patients to review the results of a cerebrospinal fluid analysis with their doctor and to discuss any treatment plans.

See also Acute lymphocytic leukemia (ALL); Brain and central nervous system tumors.

Resources

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ORGANIZATIONS

American Academy of Neurology. 1080 Montreal Ave., St. Paul, MN 55116–2325. (800) 879–1960. <http://www.aan.com>.

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Lumpectomy

Definition

A lumpectomy is a type of surgery for **breast cancer**. It is considered "breast-conserving" surgery because in a lumpectomy, only the malignant tumor and a surrounding margin of normal breast tissue are removed. Lymph nodes in the armpit (axilla) also may be removed. This procedure is called **lymph node dissection**.

Purpose

Lumpectomy is a surgical treatment for newly diagnosed breast cancer. It is estimated that at least 50% of women with breast cancer are good candidates for this procedure. The location, size, and type of tumor are of primary importance when considering breast cancer surgery options. The size of the breast is another factor the surgeon considers when recommending surgery. The patient's psychological outlook, as well as her lifestyle and preferences, should also be taken into account when treatment decisions are made.

The extent and severity of a cancer is evaluated or "staged" according to a fairly complex system. Staging considers the size of the tumor and whether the cancer has spread to other areas, such as the chest wall, the lymph nodes, and/or to distant parts of the body. Women with early stage breast cancers are usually better candidates for lumpectomy. In most cases, a course of **radiation therapy** after surgery is part of the treatment. **Chemotherapy** or antiestrogens also may be prescribed.

Many studies have compared the survival rates of women who have had removal of a breast (**mastectomy**) with those who have undergone lumpectomy and radiation therapy. The data demonstrate that for women with comparable stages of breast cancer, survival rates are similar between the two groups, but the risk of the cancer recurring in the breast is slightly higher with lumpectomy. A 2003 study confirmed that younger women who have lumpectomies have a higher risk of tumor recurrence than those who have mastectomies.

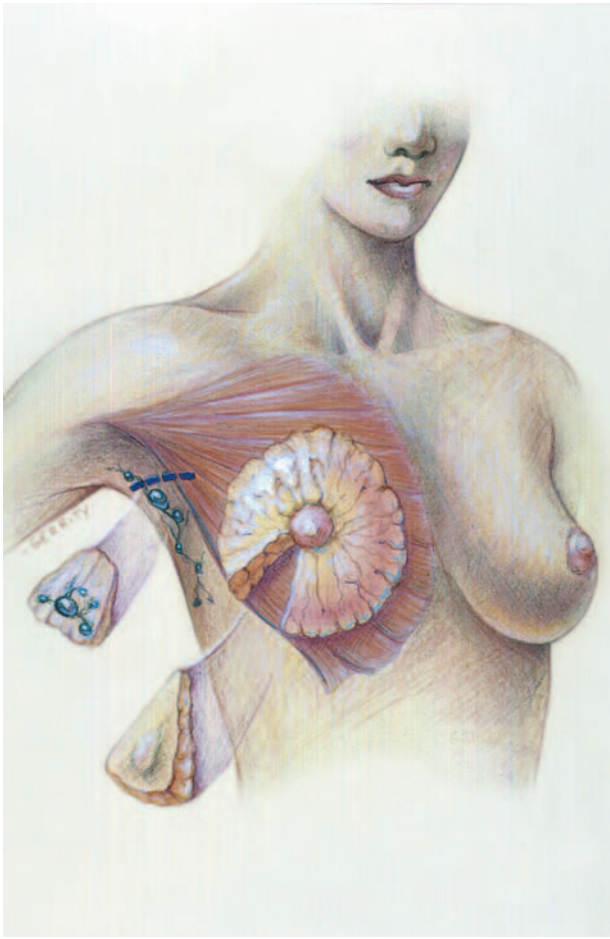
In some instances, women with later stage breast cancer may be able to have lumpectomy. Chemotherapy may be administered before surgery to decrease tumor size and the chance of spread in selected cases.

Precautions

A number of factors may prevent or prohibit a breast cancer patient from having a lumpectomy. The tumor itself may be too large or located in an area where it would be difficult to remove with good cosmetic results. Sometimes several areas of cancer are found in one breast, so the tumor cannot be removed as a single lump. A cancer that has already attached itself to nearby structures, such as the skin or the chest wall, needs more extensive surgery.

Certain medical or physical circumstances also may eliminate lumpectomy as a treatment option. Sometimes lumpectomy may be attempted, but the surgeon is unable to remove the tumor with a sufficient amount of normal tissue surrounding it. This may be termed "persistently positive margins," or "lack of clear margins," referring to the margin of unaffected tissue around the tumor. Lumpectomy is not used for women who have had a previous lumpectomy and have a recurrence of the breast cancer.

The need for radiation therapy after lumpectomy makes this surgery medically unacceptable for some women. For instance, radiation therapy cannot be



Lumpectomy is one form of breast cancer treatment in which the tumor and surrounding tissue is removed, thus preserving the breast. This illustration also shows the removal of the lymph nodes. *(Photograph by Peg Gerrity. Reproduced by permission.)*

administered to pregnant women because it may injure the fetus. If, however, delivery would be completed prior to the need for radiation, pregnant women may undergo lumpectomy. Women with collagen vascular disease, such as lupus erythematosus or scleroderma, would experience scarring and damage to their connective tissue if exposed to radiation treatments. A woman who has already had therapeutic radiation to the chest area for other reasons cannot have additional exposure for breast cancer therapy.

Some women may choose not to have a lumpectomy for other reasons. They may strongly fear a recurrence of breast cancer, and may consider a lumpectomy too risky. Others feel uncomfortable with a breast that has had a cancer, and they experience more peace of mind with the entire breast removed.

The need for radiation therapy may also be a barrier due to non-medical concerns. Some women simply fear this type of treatment and choose more extensive surgery so that radiation will not be required. The commitment of time, usually five days a week for six weeks, may not be acceptable for others. This may be due to financial, personal, or job-related constraints. Finally, in geographically isolated areas, a course of radiation therapy may require lengthy travel, and perhaps unacceptable amounts of time away from family and other responsibilities.

Description

Lumpectomy is an imprecise term. Any amount of tissue, from 1% to 50% of the breast, may be removed and called a lumpectomy. Breast conservation surgery is a frequently used synonym for lumpectomy. Partial mastectomy, quadrantectomy, segmental excision, wide excision, and tylectomy are other, less commonly used names for this procedure.

A lumpectomy is frequently done in a hospital setting (especially if lymph nodes are to be removed at the same time), but specialized outpatient facilities are sometimes preferred. The surgery is usually done while the patient is under general anesthesia. Local anesthetic with additional sedation may be used for some patients. The tumor and surrounding margin of tissue is removed and sent to the pathologist. The surgical site is closed.

If axillary lymph nodes were not removed in a prior biopsy, a second incision is made in the armpit. The fat pad that contains lymph nodes is removed from this area and is also sent to the pathologist for analysis. This portion of the procedure is called an axillary lymph node dissection; it is critical for determining the stage of the cancer. Typically, 10 to 15 nodes are removed, but the number may vary. Surgical drains may be left in place in either location to prevent fluid accumulation. The surgery may last from one to three hours.

The patient may stay in the hospital one or two days, or return home the same day. This generally depends on the extent of the surgery and the medical condition of the patient, as well as physician and patient preferences. A woman usually goes home with a small bandage. The inner part of the surgical site usually has dissolvable stitches. The skin may be sutured or stitched; or the skin edges may be held together with steristrips, which are special thin, clear pieces of tape.

Preparation

Routine preoperative preparations, such as having nothing to eat or drink the night before surgery, are typically ordered for a lumpectomy. Information about expected outcomes and potential complications is also part of preparation for lumpectomy, as it is for any surgical procedure. It is especially important that women

know about sensations they might experience after the operation, so the sensations are not misinterpreted as signs of further cancer or poor healing.

If the tumor is not able to be felt (not palpable), a pre-operative localization procedure is needed. A fine wire, or other device, is placed at the tumor site, using **x ray** or ultrasound for guidance. This is usually done in the radiology department of a hospital. The woman is most often sitting up and awake, although some sedation may be administered.

Aftercare

After a lumpectomy, patients are usually cautioned against lifting anything that weighs more than five pounds for several days. Other activities may be restricted (especially if the axillary lymph nodes were removed) according to individual needs. Pain is often enough to limit inappropriate motion. Women are often instructed to wear a well-fitting support bra both day and night for approximately one week after surgery.

Pain is usually well controlled with prescribed medication. If it is not, the patient should contact the surgeon, as severe pain may be a sign of a complication, which needs medical attention. A return visit to the surgeon is normally scheduled approximately ten days to two weeks after the operation. Studies have shown that women improve their survival rates after lumpectomy if they stop smoking.

Radiation therapy is usually started as soon as feasible after lumpectomy. Other additional treatments, such as chemotherapy or hormone therapy, may also be prescribed. The timing of these is specific to each individual patient.

Risks

The risks are similar to those associated with any surgical procedure. Risks include bleeding, infection, asymmetry, anesthesia reaction, or unexpected scarring. A lumpectomy also may cause loss of sensation in the breast. The size and shape of the breast will be affected by the operation. Fluid can accumulate in the area where tissue was removed, requiring drainage.

If lymph node dissection is performed, there are several potential complications. A woman may experience decreased feeling in the back of her armpit. She may also experience other sensations, including numbness, tingling, or increased skin sensitivity. An inflammation of the arm vein, called phlebitis, can occur. There may be injury to the nerves controlling arm motion.

KEY TERMS

Lymph node—A small mass of tissue in the form of a knot or protuberance. They are the primary source of lymph fluid, which serves in the body's defense by removing toxic fluids and bacteria.

Approximately 2% to 10% of patients develop lymphedema (swelling of the arm) after axillary lymph node dissection. This swelling of the arm can range from mild to very severe. It can be treated with elastic bandages and specialized physical therapy, but it is a chronic condition, requiring continuing care. Lymphedema can arise at any time, even years after surgery.

A new technique often eliminates the need for removing many axillary lymph nodes. **Sentinel lymph node mapping** and **biopsy** is based on the idea that the condition of the first lymph node in the network, which drains the affected area, can predict whether the cancer may have spread to the rest of the nodes. It is thought that if this first, or sentinel, node is cancer-free, there is no need to look further. Many patients with early-stage breast cancers may be spared the risks and complications of axillary lymph node dissection as the use of this approach continues to increase.

Normal results

When lumpectomy is performed, it is anticipated that it will be the definitive surgical treatment for breast cancer. Other forms of therapy, especially radiation, are often prescribed as part of the total treatment plan. A 2003 study reported that radiation of the entire breast produces better results than radiation of part of the breast. The expected outcome after lumpectomy and radiation is no recurrence of the breast cancer, however, women who have had lumpectomies, particularly those who were young at the time of treatment, should continue to see their physicians for regular breast cancer check-ups, since the cancer can recur.

Abnormal results

An unforeseen outcome of lumpectomy may be recurrence of the breast cancer, either locally or distally (in a part of the body far from the original site). Recurrence may be discovered soon after lumpectomy or years after the procedure. For this reason, it is important for patients to be regularly and closely monitored by their physicians. A 2003 report showed that magnetic resonance imaging (MRI) is accurate in detecting any cancer left in the breast after lumpectomy. Women should

continue to have regular mammograms. While the scar tissue from lumpectomy and radiation therapy can make mammograms less comfortable, a special cushion was approved by the U.S. Food and Drug Administration in 2003 that reduces discomfort in women who have had breast conserving surgery.

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Lung cancer, non-small cell

Definition

Non-small cell lung cancer (NSCLC) is a disease in which the cells of the lung tissues grow uncontrollably and form tumors.

Description

There are two kinds of lung cancers, primary and secondary. Primary lung cancer starts in the lung itself, and is divided into small cell lung cancer and non-small cell lung cancer. Small cell lung cancers are shaped like an oat and called oat-cell cancers; they are aggressive, spread rapidly, and represent 20% of lung cancers. Non-small cell lung cancer represents almost 80% of all primary lung cancers. Secondary lung cancer is cancer that starts somewhere else in the body (for example, the breast or colon) and spreads to the lungs.

The lungs

The lungs are located along with the heart in the chest cavity. The lungs are not simply hollow balloons but have a very organized structure consisting of hollow tubes, blood vessels and elastic tissue. The hollow tubes, called bronchi, are highly branched, becoming smaller and more numerous at each branching. They end in tiny, blind sacs made of elastic tissue called alveoli. These sacs are where the oxygen a person breathes in is taken up into the blood, and where carbon dioxide moves out of the blood to be breathed out.

Normal healthy lungs are continually secreting mucus that not only keeps the lungs moist, but also protects the lungs by trapping foreign particles like dust and dirt in breathed air. The inside of the lungs is covered with small hairlike structures called cilia. The cilia move in such a way that mucus is swept up out of the lungs and into the throat.

Lung cancer

Most lung cancers start in the cells that line the bronchi, and can take years to develop. As they grow larger they prevent the lungs from functioning normally. The tumor can reduce the capacity of the lungs, or block the movement of air through the bronchi in the lungs. As a result, less oxygen gets into the blood and patients feel short of breath. Tumors may also block the normal movement of mucus up into the throat. As a result, mucus builds up in the lungs and infection may develop behind the tumor. Once lung cancer has developed, it frequently spreads to other parts of the body.

The speed at which non-small cell tumors grow depends on the type of cells that make up the tumor. The following three types account for the vast majority of non-small cell tumors:

- Adenocarcinomas are the most common and often cause no symptoms. Frequently they are not found until they are advanced.
- Squamous cell carcinomas usually produce symptoms because they are centrally located and block the lungs.
- Undifferentiated large cell and giant cell carcinomas tend to grow rapidly, and spread quickly to other parts of the body.

Demographics

Worldwide, lung cancer is the most common cancer in males, and the fifth most common cancer in women. The worldwide mortality rate for patients with lung cancer is 86%. In the United States, lung cancer is the leading cause of death from cancer among both men and women. The World Health Organization estimates that the worldwide mortality from lung cancer will increase to three million by the year 2025. Of those three million deaths, almost two and a half million will result from non-small cell lung cancer.

The American Cancer Society (ACS) estimates that 173,770 Americans will develop lung cancer in 2004, 93,110 men and 80,660 women. Of these patients, 160,440 will die of the disease.

The incidence of lung cancer is beginning to fall in developed countries. This may be a result of antismoking campaigns. In developing countries, however, rates continue to rise, which may be a consequence of both industrialization and the increasing use of tobacco products.

Causes and symptoms

Causes

Tobacco smoking accounts for 87% of all lung cancers. Giving up tobacco can prevent most lung cancers. Smoking **marijuana cigarettes** is considered another risk factor for cancer of the lung. Second-hand smoke also contributes to the development of lung cancer among nonsmokers.

Certain hazardous materials that people may be exposed to in their jobs have been shown to cause lung cancer. These include asbestos, coal products, and radioactive substances. Air pollution may also be a contributing factor. Exposure to radon, a colorless, odorless gas that sometimes accumulates in the basement of homes, may cause lung cancer in a tiny minority of patients. In addition, patients whose lungs are scarred from other lung conditions may have an increased risk of developing lung cancer.

Symptoms

Lung cancers tend to spread very early, and only 15% are detected in their early stages. The chances of early detection, however, can be improved by seeking medical care at once if any of the following symptoms appear:

- a cough that does not go away
- chest pain
- shortness of breath
- recurrent lung infections, such as bronchitis or pneumonia
- bloody or brown-colored spit or phlegm (sputum)
- persistent hoarseness
- significant **weight loss** that is not due to dieting or vigorous exercise; **fatigue** and loss of appetite (anorexia)
- unexplained fever

Although these symptoms may be caused by diseases other than lung cancer, it is important to consult a doctor to rule out the possibility of lung cancer.

If lung cancer has spread to other organs, the patient may have other symptoms such as headaches, bone fractures, pain, bleeding, or blood clots.

Diagnosis

Physical examination and diagnostic tests

The doctor will first take a detailed medical history and assess risk factors. During a complete physical examination the doctor will examine the patient's throat to rule out other possible causes of hoarseness or coughing, and will listen to the patient's breathing and chest sounds.

If the doctor has reason to suspect lung cancer, particularly if the patient has a history of heavy smoking or occupational exposure to irritating substances, a chest **x ray** may be ordered to see if there are any masses in the lungs. Special imaging techniques, such as **computed tomography** (CT) scans or **magnetic resonance imaging** (MRI), may provide more precise information about the size, shape, and location of any tumors.

Sputum analysis

Sputum analysis is a noninvasive test that involves microscopic examination of cells that are coughed up from the lungs. This test can diagnose at least 30% of lung cancers, even if tumors are not visible on chest x rays. In addition, the test can detect cancer in its very early stages, before it spreads to other regions. The sputum test does not provide any information about the location of the tumor.

Lung biopsy

Lung **biopsy** is the most definitive diagnostic tool for cancer. It can be performed in three different ways. **Bronchoscopy** involves the insertion of a slender, lighted tube, called a bronchoscope, down the patient's throat and into the lungs. This test allows the doctor to see the tubes inside the lungs, and to obtain samples of lung tissue. If a needle biopsy is to be performed, the location of the tumor is first identified using a computerized tomography (CT) scan or magnetic resonance imaging (MRI). The doctor then inserts a needle through the

chest wall and collects a sample of tissue from the tumor. In the third procedure, known as surgical biopsy, the chest wall is opened up and a part of the tumor, or all of it, is removed. A doctor who specializes in the study of diseased tissue (a pathologist) examines the tumor to identify the cancer's type and stage.

Treatment team

The treatment team for patients with non-small cell lung cancer will depend on which treatment strategy is followed. For patients who are treated surgically, a thoracic surgeon will perform the procedure. These surgeons specialize in operating inside the chest cavity. Patients who require **radiation therapy** will be seen by a radiation oncologist. Patients who need **chemotherapy** will see a hematologist or oncologist. Both are doctors who specialize in cancer treatment. Chemotherapy is usually administered by oncology nurses that specialize in caring for cancer patients.

Clinical staging, treatments, and prognosis

Staging

Treatment for non-small cell lung cancer depends primarily on the stage of the cancer. Staging is a process that tells the doctor if the cancer has spread and the extent of its spread. The most commonly used treatments are surgery, radiation therapy, and chemotherapy.

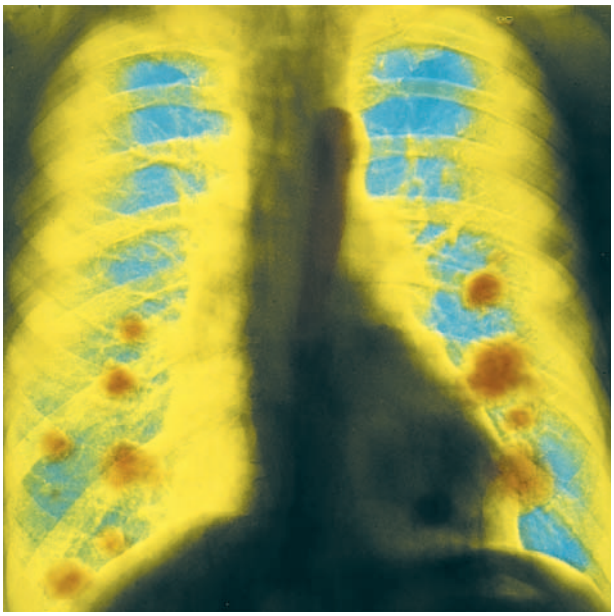
Non-small cell lung cancer has six stages:

- Occult **carcinoma**. Cancer cells have been found in the sputum, but no tumor has yet been found.
- Stage 0. A small group of cancerous cells have been found in one location.
- Stage I. The cancer is only in the lung and has not spread anywhere else.
- Stage II. The cancer has spread to nearby lymph nodes.
- Stage III. The cancer has spread to more distant lymph nodes, and/or other parts of the chest like the diaphragm.
- Stage IV. The cancer has spread to other parts of the body.

Surgery

Surgery is the standard treatment for the earlier stages of non-small cell lung cancer. The surgeon will decide on the type of surgery, depending on how much of the lung is affected. There are three different types of surgical procedures:

- Wedge resection is the removal of a small part of the lung.



False-color chest x ray showing evidence of cancerous masses (orange shadows) in both lungs. *(Copyright CNRI, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

- Lobectomy is the removal of one lobe of the lung. (The right lung has three lobes and the left lung has two lobes.)
- Pneumonectomy is the removal of an entire lung.

Lung surgery is a major procedure and patients can expect to experience pain, weakness in the chest, and shortness of breath. Air and fluid collect in the chest after surgery. As a result, patients will need help to turn over, cough, and breathe deeply. Patients should be encouraged to perform these activities because they help get rid of the air and fluid and speed up recovery. It can take patients several months before they regain their energy and strength.

Radiotherapy

Patients whose cancer has progressed too far for surgery (Stages III and IV) may receive radiotherapy. Radiotherapy involves the use of high-energy rays to kill cancer cells. It is used either by itself or in combination with surgery or chemotherapy. The amount of radiation used depends on the size and the location of the tumor.

Radiation therapy may produce such side effects as fatigue, skin rashes, upset stomach, and **diarrhea**. Dry or sore throats, difficulty in swallowing, and loss of hair (alopecia) in the treated area are all minor side effects of

radiation. These may disappear either during the course of the treatment or after the treatment is over.

Chemotherapy

Chemotherapy is also given to patients whose cancer has progressed too far for surgery. Chemotherapy is medication that is usually given intravenously to kill cancer cells. These drugs enter the bloodstream and travel to all parts of the body, killing cancer cells that have spread to different organs. Chemotherapy is used as the primary treatment for cancers that have spread beyond the lung and cannot be removed by surgery. It can also be used in addition to surgery or radiation therapy.

Chemotherapy for NSCLC has made significant advances since the early 1980s in improving the patient's quality of life as well as length of survival. Newer cytotoxic (cell-killing) agents developed in the 1990s, such as the taxanes, are typically combined with either cisplatin or carboplatin as first-line therapy for non-small cell lung cancer.

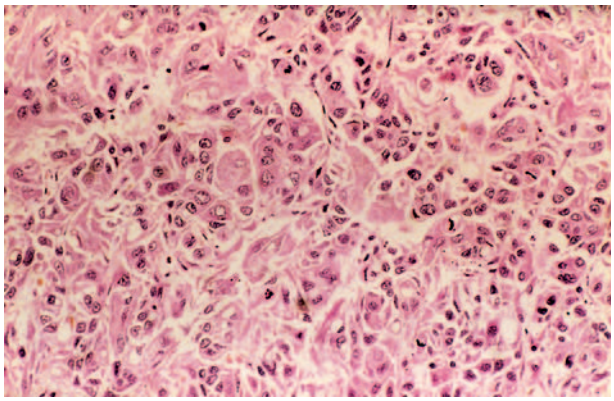
Newer drugs for lung cancer developed since 2000 include gefinitib (Iressa) and pemetrexed (Alimta). The FDA approved gefinitib in May 2003 as a treatment for patients with NSCLC who have not responded to platinum-based or taxane chemotherapy. It is taken by mouth and works by inhibiting an enzyme involved in the growth of tumor cells. Pemetrexed, which is given by injection, was approved by the FDA in February 2004 for the treatment of mesothelioma, a type of lung cancer caused by exposure to asbestos fibers. However, the drug appears to be effective in treating other types of lung cancer as well.

Chemotherapy is also used as palliative treatment for non-small cell lung cancer. Palliative refers to any type of therapy that is given to relieve the symptoms of a disease but not to cure it.

Chemotherapy for non-small cell lung cancer often has severe side effects, including **nausea and vomiting**, hair loss, anemia, weakening of the immune system, and sometimes **infertility**. Most of these side effects end when the treatment is over. Other medications can be given to lessen the unpleasant side effects of chemotherapy.

Prognosis

The prognosis for non-small cell lung cancer is better if the disease is found early, and removed surgically. For patients whose disease is caught in Stage I, the survival rate five years after surgery ranges from 60% to 80%. Up to 55% of Stage II patients are alive after five years, but only about 30% of Stage III patients survive five years. Unfortunately, 85% of patients already have at least Stage III cancer by the time they are diagnosed. Many of these patients have disease that is too advanced for surgery. Despite treatment with radiotherapy and chemotherapy, the five-year survival for patients with inoperable disease is extremely low.



Large-cell anaplastic carcinoma of the lung. *(Copyright Biophoto Associates, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Alternative and complementary therapies

Because non-small cell lung cancer has a poor prognosis with conventional medical treatment, many patients are willing to try complementary and alternative therapies. These therapies are used to try to reduce stress, ease side effects and symptoms, or control disease. Two treatments sometimes used are shark cartilage and mistletoe. Although shark cartilage is thought to interfere with the tumor's blood supply, **clinical trials** have so far been inconclusive. Mistletoe is a poisonous plant that has been shown to kill cancer cells in the laboratory. Again, however, clinical trials with cancer patients have been inconclusive.

Patients who decide to try complementary and alternative therapies should tell their doctors. Some of these therapies may interfere with conventional treatment.

Coping with cancer treatment

The side effects associated with treatment of non-small cell lung cancer can be severe. Patients should ask their doctors about medications to treat nausea and vomiting, and other side effects. It is particularly important to eat a nutritious diet and to drink plenty of fluids. In addition, most patients report feeling very tired and should get plenty of rest.

KEY TERMS

Bronchi—The tubes that carry air into the lungs.

Lymph—Clear fluid containing white blood cells that is collected from the tissues of the body and flows in vessels called the lymphatic system.

Lymph node—Small oval-shaped filters in the lymphatic system that trap bacteria and other unwanted particles to ensure their removal from the body.

Palliative—Referring to any type of treatment that is given to relieve the symptoms of a disease rather than to cure it.

Respiratory distress—A condition in which patients with lung disease are not able to get enough oxygen.

QUESTIONS TO ASK THE DOCTOR

- What type of lung cancer do I have?
- Has the cancer spread?
- What are the treatment options?
- Is there a clinical trial I can participate in?
- What is my prognosis?

Patients should consider joining local support groups with people who are coping with the same experiences. Many people with cancer find they can share thoughts and feelings with group members that they do not feel comfortable sharing with friends or family. Support groups are also a good source of information about coping with cancer.

Clinical trials

Patients diagnosed with non-small cell lung cancer should discuss participating in clinical trials with their doctor. There are many clinical trials currently underway that are investigating all different stages of the disease. These trials are studying various new treatment options including:

- Chemotherapy with new drugs, and combinations of drugs
- Courses of chemotherapy prior to surgery
- Radiotherapy after surgery
- Chemotherapy and radiotherapy in combination

Information on open clinical trials is available on the Internet from the National Cancer Institute at <http://cancertrials.nci.nih.gov>.

Prevention

The best way to prevent lung cancer is not to start smoking or to quit smoking. Secondhand smoke from other people's tobacco should also be avoided. Appropriate precautions should be taken when working with cancer-causing substances (carcinogens). Testing houses for the presence of radon gas, and removing asbestos from buildings have also been suggested as preventive strategies.

Special concerns

Respiratory distress

Patients who are having difficulty breathing because of non-small cell lung cancer are often unable to get enough oxygen and suffer from respiratory distress. These patients may begin breathing more quickly and wheezing. Patients will usually be given oxygen and medications such as morphine that will help them breathe more easily.

Follow-up

Regular checkups after treatment for non-small cell lung cancer are extremely important. Patients who have been treated for lung cancer should report any health problems to their doctor immediately to ensure quick treatment if the cancer has returned.

See also Cigarettes; Smoking cessation.

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American Lung Association. (800) 586-4872. <http://www.lungusa.org>.

National Cancer Institute (National Institutes of Health). 9000 Rockville Pike, Bethesda, MD 20892. (800) 422-6237. <http://www.nci.nih.gov>.

National Center for Complementary and Alternative Medicine (National Institutes of Health). PO Box 8218, Silver Spring, MD 20907-8218. (888) 644-6226. <http://nccam.nih.gov>.

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Lung cancer, small cell

Definition

Small cell lung cancer is a disease in which the cells of the lung tissues grow uncontrollably and form tumors.

Description

Lung cancer is divided into two main types: small cell and non-small cell. Small cell lung cancer is the least common of the two, accounting for only about 20% of all lung cancers. In the past, the disease was called oat cell cancer because, when viewed under a microscope, the cancer cells resemble oats. This type of lung cancer grows quickly and is more likely to spread to other organs in the body.

The lungs are located along with the heart in the chest cavity. The lungs are not simply hollow balloons, but have a very organized structure consisting of hollow tubes, blood vessels, and elastic tissue. The hollow tubes, called bronchi, are multi-branched, becoming smaller and more numerous at each branching. They end in tiny, blind sacs made of elastic tissue called alveoli. These sacs are where the oxygen a person breathes in is taken up into the blood, and where carbon dioxide moves out of the blood to be breathed out.

Normal, healthy lungs are continually secreting mucus that not only keeps the lungs moist, but also protects the lungs by trapping foreign particles like dust and dirt in breathed air. The inside of the lungs is covered with small, hair-like structures called cilia. The cilia move in such a way that mucus is swept up out of the lungs and into the throat.

Small cell lung tumors usually start to develop in the central bronchi. They grow quickly and prevent the lungs from functioning at their full capacity. Tumors may block the movement of air through the bronchi in the lungs. As a result, less oxygen gets into the blood and patients feel short of breath. Tumors may also block the normal movement of mucus into the throat. As a result, mucus builds up in the lungs and infection may develop behind the tumor.

Demographics

Lung cancer is a growing global epidemic. Worldwide, lung cancer is the second most common cancer among both men and women and is the leading cause of cancer death in both sexes. The worldwide mortality rate for patients with lung cancer is 86%. Of the 160,000 deaths from lung cancer that occur annually in the United

States, about 40,000 are caused by small cell lung cancer. Although there are differences in mortality rates between ethnic groups, this is mainly due to differences in smoking habits.

Causes and symptoms

Causes

Tobacco smoking accounts for nearly 90% of all lung cancers. The risk of developing lung cancer is increased for smokers who start at a young age, and for those who have smoked for a long time. The risk also increases as more **cigarettes** are smoked, and when cigarettes with higher tar content are smoked. Smoking **marijuana** cigarettes is also a risk factor for lung cancer. These cigarettes have a higher tar content than tobacco cigarettes.

Certain hazardous materials that people may be exposed to in their jobs have been shown to cause lung cancer. These include asbestos, coal products, and radioactive substances. Air pollution may also be a contributing factor. Exposure to radon, a colorless, odorless gas that sometimes accumulates in the basement of homes, may cause lung cancer in some patients. In addition, patients whose lungs are scarred from other lung conditions may have an increased risk of developing lung cancer.

Although the exact cause of lung cancer is not known, people with a family history of lung cancer appear to have a slightly higher risk of contracting the disease.

Symptoms

Small cell lung cancer is an aggressive disease that spreads quickly. Symptoms depend on the tumor's location within the lung, and on whether the cancer has spread to other parts of the body. More than 80% of small cell lung cancer patients have symptoms for only three months or less, and few cases are detected early. The following symptoms are the most commonly reported by small cell lung cancer patients at the time of their diagnosis:

- a cough that does not go away
- chest pain
- shortness of breath and wheezing
- persistent hoarseness
- **fatigue** and loss of appetite (anorexia). Although some patients may experience bloody spit or phlegm, this symptom is more commonly seen in patients with other types of lung cancer.

Small cell tumors often press against a large blood vessel near the lungs called the superior vena cava (SVC), causing a condition known as SVC syndrome. This condition may cause patients to retain water, cough, and have shortness of breath. Because small cell lung cancer often spreads quickly to the bones and central nervous system, patients may also have **bone pain**, headaches, and seizures.

Diagnosis

If lung cancer is suspected, the doctor will take a detailed medical history that checks both symptoms and risk factors. During a complete physical examination, the doctor will examine the patient's throat to rule out other possible causes of hoarseness or coughing, and listen to the patient's breathing and the sounds made when the patient's chest and upper back are tapped. A chest **x ray** may be ordered to check for masses in the lungs. Special imaging techniques, such as **computed tomography** (CT) scans or **magnetic resonance imaging** (MRI), may provide more precise information about the size, shape, and location of any tumors.

Sputum analysis involves microscopic examination of the cells that are either coughed up from the lungs, or are collected through a special instrument called a bronchoscope. The sputum test does not, however, provide any information about the location of the tumor and must be followed by other tests.

Lung **biopsy** is the most definitive diagnostic tool for cancer. It can be performed in several different ways. The doctor can perform a **bronchoscopy**, which involves the insertion of a slender, lighted tube, called a bronchoscope, down the patient's throat and into the lungs. In addition to viewing the passageways of the lungs, the doctor can use the bronchoscope to obtain samples of the lung tissue. In another procedure known as a needle biopsy, the location of the tumor is first identified using a CT scan or MRI. The doctor then inserts a needle through the chest wall and collects a sample of tissue from the tumor. In the third procedure, known as surgical biopsy, the chest wall is opened up and a part of the tumor, or all of it, is removed for examination.

Treatment team

Small cell lung cancer patients are usually treated with a combination of **chemotherapy** and radiotherapy. Patients will usually see an oncologist (cancer specialist) who will supervise their chemotherapy, while a radiation oncologist will supervise their radiotherapy. Oncology nurses that specialize in caring for cancer patients usually administer chemotherapy. The few patients who undergo surgery will see a thoracic surgeon who specializes in operating in the chest cavity.

Clinical staging, treatments, and prognosis

Staging

Staging procedures are important in lung cancer because they tell doctors whether patients have disease only in their lungs, or whether the cancer has spread to other parts of the body. To establish the cancer stage, doctors have to perform various tests. These may include **bone marrow aspiration and biopsy**, CT scans of the chest and abdomen, MRI scans of the brain, and radionuclide bone scans. All of these tests determine the extent to which the cancer has spread. Once the stage is determined, doctors can decide on a course of treatment, and can have a better idea of the patient's prognosis.

Unlike other types of lung cancer, the staging of small cell lung cancer is relatively simple. This is because approximately 70% of patients already have metastatic disease when they are diagnosed, and small differences in the amount of tumor found in the lungs do not change the prognosis. Small cell lung cancer is usually divided into three stages:

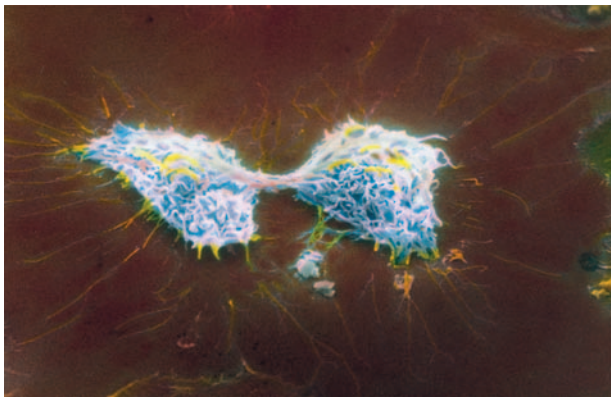
- Limited stage: The cancer is found only in one lung and in lymph nodes close to the lung.
- Extensive stage: The cancer has spread beyond the lungs to other parts of the body.
- Recurrent stage: The cancer has returned following treatment.

Treatment

Without treatment, small cell lung cancer has the most aggressive clinical course of any type of pulmonary tumor, with median survival from diagnosis of only 2–4 months. Compared with other cell types of lung cancer, small cell lung cancer has a greater tendency to be widely disseminated by the time of diagnosis, but is much more responsive to chemotherapy and irradiation.

Treatment of small cell lung cancer depends on whether the patient has limited, extensive, or recurrent disease. Treatment usually involves radiotherapy and chemotherapy. Surgery is rarely used for this type of lung cancer because the tumor is usually too advanced.

Patients with limited-stage disease are usually treated with chemotherapy. Combinations of two or more drugs have a better effect than treatment with a single drug. Up to 90% of patients with this stage of disease will respond to chemotherapy. The chemotherapy most commonly prescribed is a combination of the drugs **etoposide** (Vepesid) and **cisplatin** (Platinol). Combining chemotherapy with chest radiotherapy and/or occasionally surgery has also prolonged survival for limited-stage patients.



Lung cancer cells dividing. *(Custom Medical Stock Photo. Reproduced by permission.)*

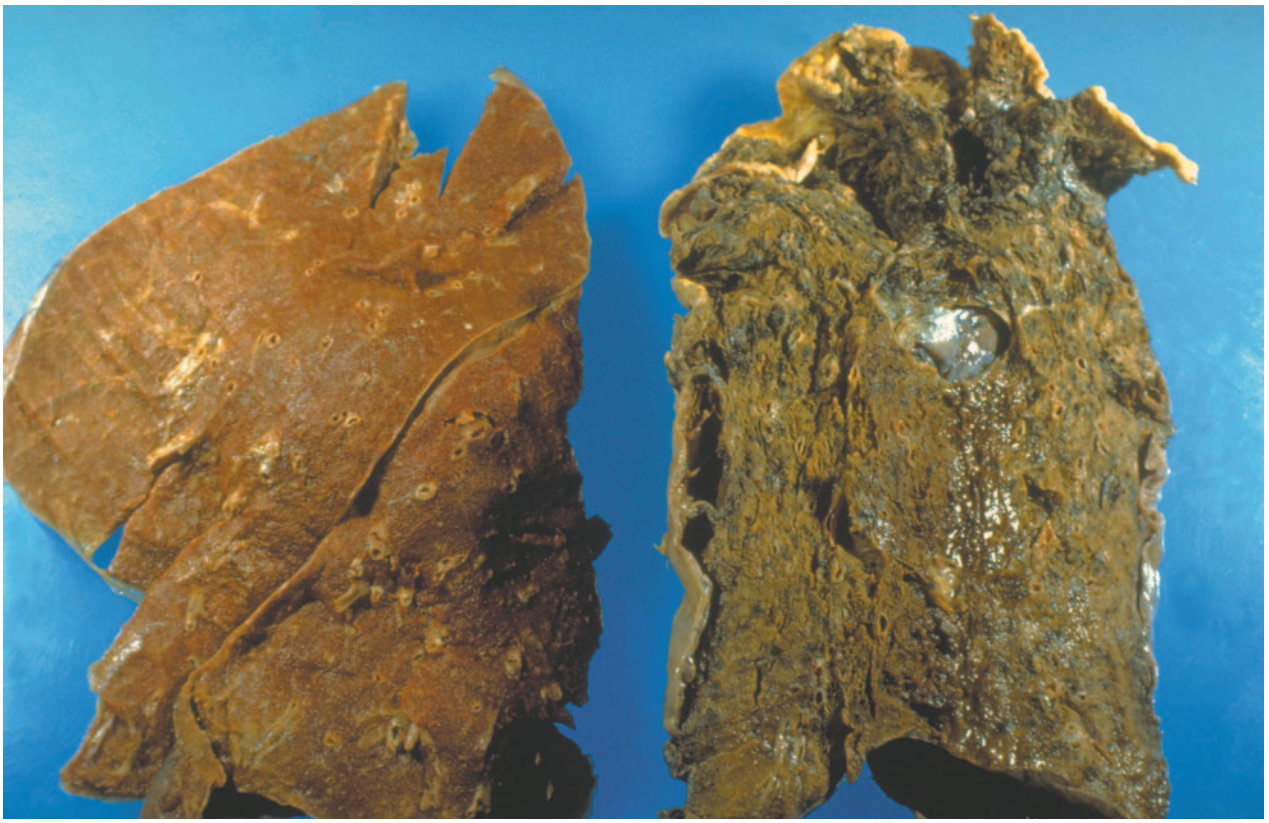
In addition to chest radiotherapy, some patients are also treated with **radiation therapy** to the brain, even if no cancer is found there. This treatment, called prophylactic cranial irradiation (PCI), is given to prevent tumors from forming in the brain. The combination of etoposide and cisplatin chemotherapy with chest radiation therapy and PCI has increased the two-year survival of limited-stage small cell lung cancer patients to almost 50%.

Combinations of different chemotherapy agents are also used for treating extensive-stage small cell lung cancer. However, compared with limited-stage patients, the percentage of extensive-stage patients who respond to therapy is lower. Commonly used drug combinations include **cyclophosphamide** (Cytoxan), **doxorubicin** (Adriamycin), and **vincristine** (Oncovin), or etoposide and cisplatin. The addition of radiation therapy to chemotherapy does not improve survival in these patients. However, radiation therapy is used for the palliative (pain relief) treatment of symptoms of metastatic lung cancer, particularly brain and bone tumors.

Patients who have recurrent small cell lung cancer often become resistant to chemotherapy. These patients are treated with palliative radiotherapy. Their doctors may also recommend that they take part in clinical trials of a new therapy. Patients whose relapse occurs more than six months after their initial treatment, however, may still respond to traditional chemotherapy.

Prognosis

Small cell lung cancer is a very aggressive disease. Without treatment, limited-stage patients will survive for three to six months, while extensive-stage patients will survive six to 12 weeks. However, small cell lung cancer is much more responsive to chemotherapy and radiation therapy than other types of lung cancer. Among patients treated with chemotherapy, 70–90% have a major response to treatment.



A normal lung (left) and the lung of a cigarette smoker (right). *(Photograph by A. Glauberman, National Audubon Society Collection/ Photo Researchers, Inc. Reproduced by permission.)*

Survival in patients responding to therapy is four to five times longer than in patients without treatment. In addition, two years after the start of therapy, about 10% of patients remain free of disease. In general, women tend to have a better prognosis than men. Patients whose disease has spread to the central nervous system or liver have a much worse prognosis. Although the overall survival at five years is 5% to 10%, survival is higher in patients with limited stage disease. About 70% of patients who are disease free after two years do not relapse. After five to 10 disease-free years, relapses are rare.

Alternative and complementary therapies

Many cancer patients have tried using shark cartilage to treat their disease. Shark cartilage is thought to interfere with the tumor's blood supply. A clinical trial using this treatment in lung cancer patients is ongoing. Information on this and other alternative treatments is available on the Internet from the National Center for Complementary and Alternative Medicine.

Patients who decide to try complementary and alternative therapies should tell their doctor. Some of these therapies may interfere with conventional treatment.

Coping with cancer treatment

The side effects associated with treatment of small cell lung cancer can be severe. Patients should ask their doctor about medications to treat **nausea and vomiting** and other side effects. It is particularly important to eat a nutritious diet and to drink plenty of fluids. In addition, most patients report feeling very tired and should get plenty of rest.

Clinical trials

Most of the improvements in the survival of patients with small cell lung cancer are the result of **clinical trials**. Ongoing trials are investigating new chemotherapy and radiotherapy regimens. In addition, entirely new types of therapy, such as gene therapy and biological therapy, are now being tested. Patients with a lung cancer diagnosis should ask their doctor about participating in a clinical trial.

KEY TERMS

Bronchi—Hollow tubes that carry air into the lungs.

PCI—A type of radiotherapy that is used to prevent tumors from growing in the brain.

Radionuclide bone scan—A test that tells if cancer has spread to the bones.

Superior vena cava (SVC) syndrome—A condition seen in lung cancer patients where the tumor presses against a large blood vessel and causes various symptoms.

Information on open clinical trials is available on the Internet from the National Cancer Institute at <http://cancertrials.nci.nih.gov>.

Prevention

The best way to prevent lung cancer is either not start smoking, or quit smoking. Secondhand smoke from other people's tobacco should also be avoided. Appropriate precautions should be taken when working with substances that can cause cancer (carcinogens). Testing houses for the presence of radon gas, and removing asbestos from buildings have also been suggested as preventive strategies.

Special concerns

Small cell lung cancer can cause several hormonal disorders. About 40% of patients begin to secrete an anti-diuretic hormone at the wrong time. This hormone causes the body to retain water, which may result in the patient experiencing confusion, seizures, or coma. Less common are the development of **Cushing's syndrome** and the **Eaton-Lambert syndrome**. Symptoms of Cushing's syndrome include obesity, severe fatigue, high blood pressure, backache, high blood sugar, easy bruising, and bluish-red stretch marks on the skin. Eaton-Lambert syndrome is a neuromuscular disorder that causes muscle weakness, fatigue, and a tingling sensation on the skin. All of these hormonal disorders usually diminish after the lung tumor is successfully treated.

See also Smoking cessation; Superior vena cava syndrome.

Resources

BOOKS

Pass, Harvey I., et al. *Lung Cancer Principles and Practice*. Philadelphia: Lippincott Williams and Wilkins, 2000.

QUESTIONS TO ASK THE DOCTOR

- What type of lung cancer do I have?
- Has the cancer spread?
- What are the treatment options?
- Should I consider a clinical trial?

PERIODICALS

Adjei, Alex A., et al. "Current Guidelines for the Management of Small Cell Lung Cancer." *Mayo Clinic Proceedings* 74 (August 1999): 809–16.

Sandler, Alan. "Extensive Small Cell Lung Cancer: A Treatment Overview." *Oncology* 14, no. 7, Supplement 5 (July 2000): 49–55.

Tamura, Tomohide. "New State of the Art in Small Cell Lung Cancer." *Oncology* 15, no. 1, Supplement 1 (January 2001): 8–10.

ORGANIZATIONS

Alliance for Lung Cancer Advocacy, Support, and Education. P.O. Box 849, Vancouver, WA 98666. (800) 298-2436. <http://www.alcase.org>.

American Lung Association. (800) 586–4872. <http://www.lungusa.org>.

National Cancer Institute (National Institutes of Health). 9000 Rockville Pike, Bethesda, MD 20892. (800) 422–6237. <http://www.nci.nih.gov>.

National Center for Complementary and Alternative Medicine (National Institutes of Health). P.O. Box 8218, Silver Spring, MD 20907-8218. (888) 644–6226. <http://nccam.nih.gov>.

Lata Cherath, Ph.D.
Alison McTavish, M.Sc.

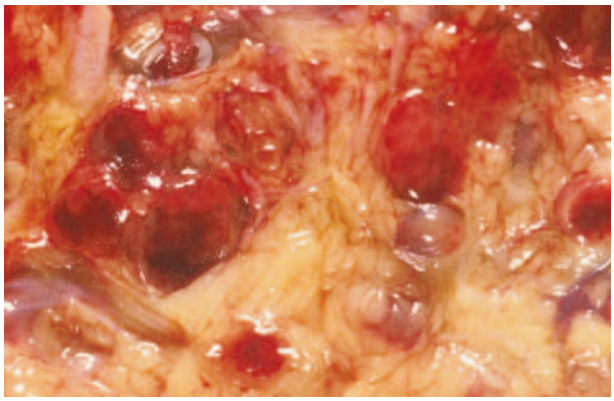
Lung metastasis *see* **Metastasis**

Lung surgery *see* **Lobectomy; Pneumonectomy; Thoracotomy**

Lymph node biopsy

Definition

A lymph node biopsy is a procedure in which all or part of a lymph node is removed and examined to determine if there is cancer within the node.



Close-up view of normal lymph nodes and fatty tissue. *(Custom Medical Stock Photo. Reproduced by permission.)*

Purpose

The lymph system is the body's primary defense against infection. It consists of the spleen, tonsils, thymus, lymph nodes, lymph vessels, and the clear, slightly yellow fluid called lymph. These components produce and transport white blood cells called lymphocytes and macrophages that rid the body of infection. The lymph system is also involved in the production of antibodies. Antibodies are proteins that fight bacteria, viruses, and other foreign materials that enter the body.

The lymph vessels are similar to veins, only instead of carrying blood as veins do, they circulate lymph to most tissues in the body. Lymph nodes are about 600 small, bean-shaped collections of tissue found along the lymph vessel. They produce cells and proteins that fight infection, and clean and filter lymph. Lymph nodes are sometimes called lymph glands, although they are not true glands. When someone talks about having swollen glands, they are actually referring to lymph nodes.

Normal lymph glands are no larger than 0.5 in (1.3 cm) in diameter and are difficult to feel. However, lymph nodes can enlarge to greater than 2.5 in (6 cm) and can become sore. Most often the swelling is caused by an infection, but it can also be caused by cancer.

Cancers can metastasize (spread) through the lymph system from the site of the original tumor to distant parts of the body where secondary tumors are formed. The purpose of a lymph node biopsy is to determine the cause of the swelling and/or to see if cancer has begun to spread through the lymph system. This information is important in staging the cancer and devising a treatment plan.

Precautions

Women who are pregnant should inform their doctor before a lymph node biopsy, although pregnancy will not affect the results.

Description

There are three kinds of lymph node biopsy. **Sentinel lymph node mapping** and biopsy is a promising new technique that is discussed in its own entry. Fine needle aspiration (FNA) biopsy, often just called needle biopsy, is done when the lymph node of interest is near the surface of the body. A hematologist (a doctor who specializes in blood diseases) usually performs the test. In FNA biopsy, a needle is inserted through the skin and into the lymph node, and a sample of tissue is drawn out of the node. This material is preserved and sent to the laboratory for examination.

Advantages of a needle biopsy are that the test is minimally invasive. Only a local anesthetic is used, the procedure generally takes less than half an hour, and there is little pain afterwards. The disadvantage is that cancer may not be detected in the small sample of cells removed by the needle.

Open lymph node biopsy is a surgical procedure. It is done by a surgeon under general anesthesia on lymph nodes in the interior of the body and under local anesthesia on surface lymph nodes where FNA biopsy is considered inadequate. Once there is adequate anesthesia, the surgeon makes a small cut and removes either the entire lymph node or a slice of tissue that is then sent to the laboratory for examination. Results in both kinds of biopsies take one to three days.

Open biopsy can be advantageous in that it is easier to detect and identify the type of cancer in a large piece of tissue. Also, lymph nodes deep in the body can be sampled. Disadvantages include a longer recovery time, soreness at the biopsy site for several days, and the use of deeper anesthesia, increasing the risks to the patient. The procedure is done in a hospital or outpatient surgery center and takes about an hour, with additional time to recover from general anesthesia.

Preparation

No particular preparation is necessary for a needle biopsy. For an open biopsy, patients need standard preoperative blood tests and other tests to evaluate general health. The doctor should be informed about any medications (prescription, non-prescription, or herbal) the patient is taking, as well as past bleeding problems or allergies to medication or anesthesia.

KEY TERMS

Lymph nodes—Small, bean-shaped organs located throughout the lymphatic system. The lymph nodes store special cells that can trap cancer cells or bacteria that are traveling through the body in lymph. Also called lymph glands.

Lymphocytes—Small white blood cells that bear the major responsibility for carrying out the activities of the immune system; they number about 1 trillion.

Malignant—Cancerous. Cells tend to reproduce without normal controls on growth and form tumors or invade other tissues.

Spleen—An organ located at the left side of the stomach that acts as a reservoir for blood cells and produces lymphocytes and other products involved in fighting infection.

Thymus—An organ near the base of the neck that produces cells that fight infection. It is at its largest at puberty, then declines in size and function during adult life.

Tonsils—Small masses of tissue at the back of the throat.

Aftercare

Little aftercare is needed in a needle biopsy other than a bandage to keep the biopsy site clean. Patients who have general anesthesia for an open biopsy often feel drowsy and tired for several days following the procedure, and should not plan to drive home after biopsy. The incision site must be kept clean and dry, and a follow-up visit to check on healing is usually necessary.

Risks

There are few risks associated with lymph node biopsy. The main risks are excessive bleeding (usually only in people with blood disorders) and allergic reaction to general anesthesia (rare). Occasionally the biopsy site becomes infected.

Normal results

Normal lymph nodes are small and flat. When examined under the microscope, they show no signs of cancer or infection.

Abnormal results

Abnormal lymph nodes are usually enlarged and contain cancerous (malignant) cells and/or show signs of infection.

QUESTIONS TO ASK THE DOCTOR

- What kind of biopsy are you going to do?
- What will this tell me about my cancer?
- If you are doing an open biopsy, will you be removing any other structures at the same time?
- If you are, how will that affect my recovery from the operation?

See also Lymph node dissection; Radical neck dissection.

Resources

ORGANIZATIONS

American Cancer Society. National Headquarters, 1599 Clifton Road NE, Atlanta, GA 30329. 800(ACS)-2345). <http://www.cancer.org>.

Cancer Information Service. National Cancer Institute, Building 31, Room 10A19, 9000 Rockville Pike, Bethesda, MD 20892. (800)4-CANCER. <http://www.nci.nih.gov/cancerinfo>.

OTHER

ThriveOnline. [cited June 12, 2001]. <http://thriveonline.oxygen.com/medical/library/article/003933.html>.

Tish Davidson, A.M.

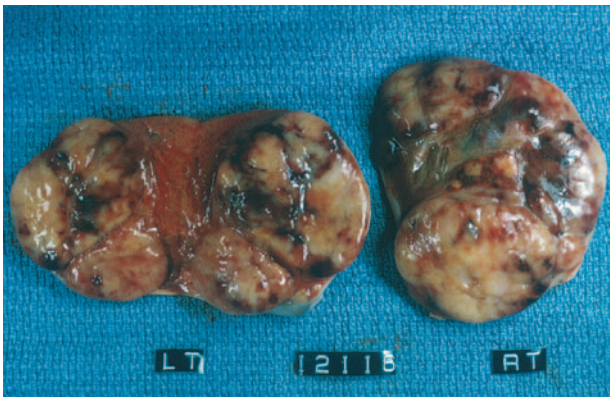
Lymph node dissection

Definition

Lymph node dissection (lymphadenectomy) is the surgical removal of lymph nodes in order to assess the spread of cancer.

Purpose

The lymph system is the body's primary defense against infection. It consists of the spleen, tonsils, thymus, lymph nodes, lymph vessels, and the clear, slightly yellow fluid called lymph. These components produce and transport cells and proteins that help rid the body of infection.



Diseased lymph nodes. *(Custom Medical Stock Photo. Reproduced by permission.)*

The lymph vessels are similar to veins, only instead of carrying blood as veins do, they circulate lymph to tissues in the body. There are about 600 small, bean-shaped collections of tissue found along the lymph vessels. These are called lymph nodes. They produce cells and proteins that fight infection. They also clean and filter foreign cells, such as bacteria or cancer cells, out of the lymph.

Cancer cells can break off from the original tumor and metastasize (spread) through the lymph system to distant parts of the body, where secondary tumors are formed. The purpose of a lymph node dissection is to remove the lymph nodes that have trapped cancer cells so that the extent of spread can be determined. Lymph node dissection is done for many different types of cancers, including cancers of the head and neck, breast, prostate, testes, bladder, colon, and lung.

About 200 lymph nodes are in the head and neck and another 30 to 50 are in the armpit. More are located in the groin area. Lymph nodes are sometimes called lymph glands, although they are not true glands. When someone talks about having swollen glands, they are referring to swollen lymph nodes.

Normally lymph nodes are no larger than 0.5 in (1.3 cm) in diameter and are difficult to feel. However, when lymph nodes trap bacteria or cancer cells, they can increase in size to greater than 2.5 in (6 cm). Most often, hot and painful swollen nodes are caused by trapped bacteria. Swollen lymph nodes caused by cancer are usually painless.

Precautions

This operation usually will not be performed if the cancer has already metastasized to another site. In this case, removing the lymph nodes will not effectively contain the cancer. As with any surgery, women who are pregnant should inform their doctors before a lymph node dissection.

Description

Lymph node dissection is usually done by a surgeon in a hospital setting, under general anesthesia. An incision is made and tissue is pulled back to reveal the lymph nodes. The surgeon is guided in what to remove by the location of the original cancer. Sample lymph nodes may be sent to the laboratory for examination. If the excised nodes do contain malignant cells, this would indicate that the cancer has spread beyond the original site, and recommendations can then be made regarding further therapy.

Preparation

Tests may be done before the operation to determine the location of the cancer and which nodes should be removed. These tests may include lymph node biopsies, CT (**computed tomography**) scans, and MRI scans. In addition, standard pre-operative blood and liver function tests are performed. The patient will meet with an anesthesiologist before the operation, and should notify the anesthesiologist about all drug allergies and all medication (prescription, non-prescription, or herbal) that he or she is taking.

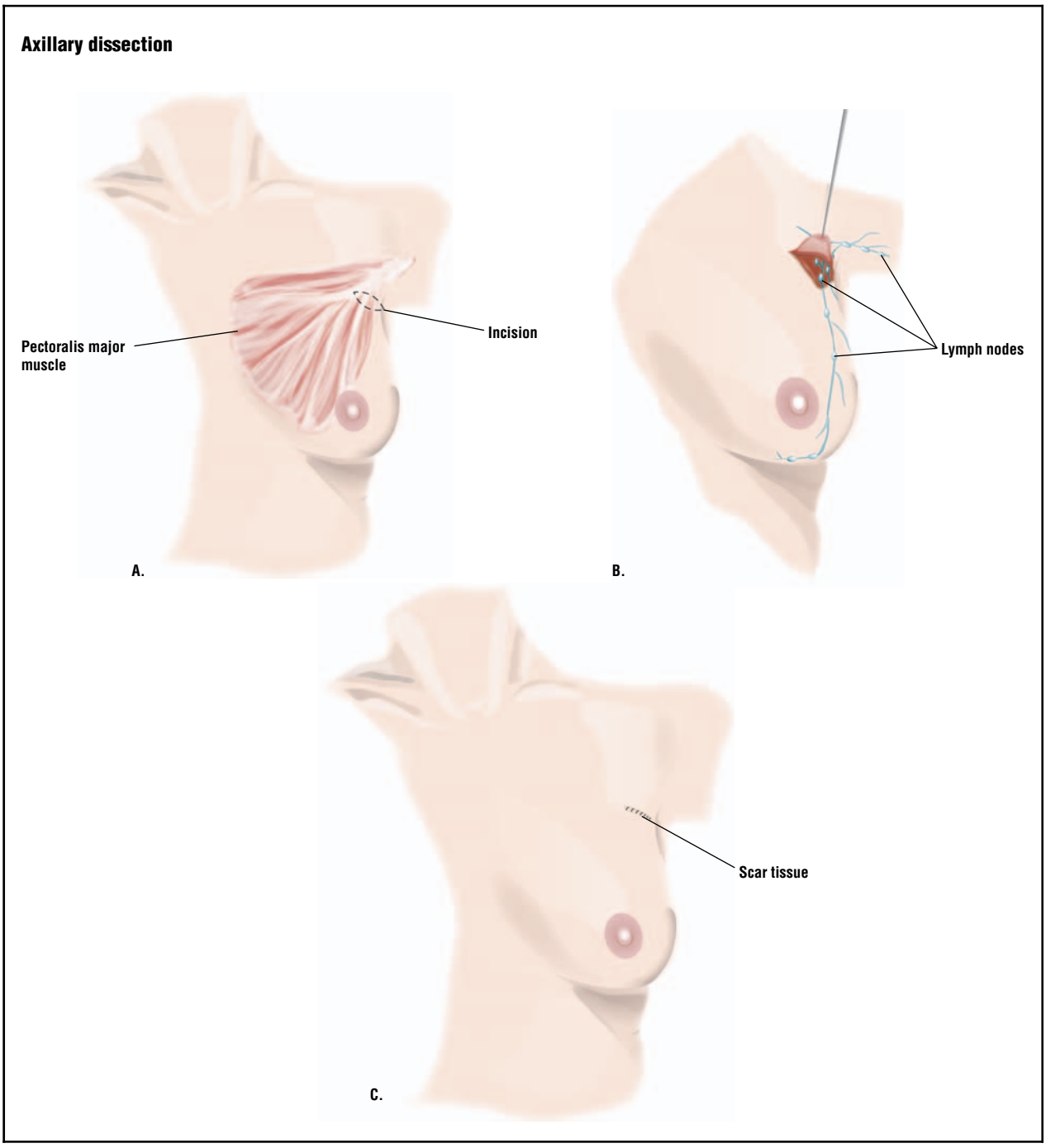
Aftercare

How long a person stays in the hospital after lymph node dissection depends on how many lymph nodes were removed, their location, and whether surgery to remove the primary tumor or other structures was performed at the same time. Drains are inserted under the skin to remove the fluid that accumulates after the lymph nodes have been removed, and patients are usually able to return home with the drains still in place. Some patients are able to leave the same day or the day following the procedure.

An accumulation of lymph fluid that causes swelling, a condition known as lymphedema, is the most feared side effect of lymph node dissection. If swelling occurs, patients should consult their doctors immediately. Swelling may indicate that a new tumor is blocking a lymph vessel, or that a side effect of lymph node dissection is present. Treatment for lymphedema in people with cancer is different than treatment of lymphedema that arises from other causes. In cancer patients, it is essential to alleviate swelling without spreading cancer cells to other parts of the body, therefore an oncologist (cancer specialist) should be consulted before beginning any treatment.

Risks

People who have lymph nodes removed are at increased risk of developing lymphedema, which can



(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)

occur in any part of the body where lymph accumulates in abnormal quantities. When the amount of fluid exceeds the capacity of the lymph system to move it through the body, it leaks into the tissues and causes them to swell. Removing lymph nodes and lymph vessels through lymph node dissection increases the likelihood that the capacity of the lymph transport system will be exceeded.

Lymphedema can occur days or weeks after lymph node dissection. **Radiation therapy** also increases the chance of developing lymphedema, so those people who have radiation therapy following lymph node dissection are at greatest risk of experiencing this side effect. Lymphedema slows healing, causes skin and tissue damage, and when left untreated can result in the

KEY TERMS

Computed tomography (CT or CAT) scan—Using x rays taken from many angles and computer modeling, CT scans help determine the size and location of tumors and provide information on whether they can be surgically removed.

Magnetic resonance imaging (MRI)—MRI uses magnets and radio waves to create detailed cross-sectional pictures of the interior of the body.

Malignant—Cancerous. Cells tend to reproduce without normal controls on growth and form tumors or invade other tissues.

Metastasize—Spread of cells from the original site of the cancer to other parts of the body where secondary tumors are formed.

QUESTIONS TO ASK THE DOCTOR

- How will you determine which lymph nodes should be removed?
- How should I prepare for this procedure?
- Are there precautions I can take to help prevent lymphedema?
- How will lymph node dissection affect my daily life?
- Will you be removing anything else besides lymph nodes during this operation?
- About how long will I have to stay in the hospital?
- Will having my lymph nodes removed increase my chances of getting infections?

development of hard or fibrous tissue. People with lymphedema are also at risk for repeated infection, because pools of lymph in the tissues provide a perfect spot for bacteria to grow. In severe cases, untreated lymphedema can develop into a rare form of cancer called lymphangiosarcoma.

Other risks associated with lymph node dissection are the same as for all major surgery: potential bleeding, infection, and allergic reaction to anesthesia.

Normal results

Normal lymph nodes are small and flat and show no cancerous cells under the microscope.

Abnormal results

Abnormal lymph nodes are enlarged and show malignant cells when examined under the microscope.

See also Lymph node biopsy; Radical neck dissection.

Resources

ORGANIZATIONS

American Cancer Society, National Headquarters. 1599 Clifton Rd. NE, Atlanta, GA 30329. 800(ACS)-2345. <http://www.cancer.org>.

Cancer Information Service. National Cancer Institute. Building 31, Room 10A19, 9000 Rockville Pike, Bethesda, MD 20892. (800) 4-CANCER. <http://www.nci.nih.gov/cancerinfo/index.html>.

National Lymphedema Network. Latham Square, 1611 Telegraph Ave., Suite 1111, Oakland, CA 94612-2138. (800) 541-3259. <http://www.lymphnet.org>.

Tish Davidson, A.M.

Lymphangiogram, lymph node angiogram
see Lymphangiography

Lymphangiography

Definition

Lymphangiography is a type of diagnostic testing technique in which x rays (called lymph node angiograms) and the injection of a contrast medium (a substance that provides a contrast between the tissue or organ being filmed and the medium) are used to visualize lymphatic circulation and the lymph nodes.

Purpose

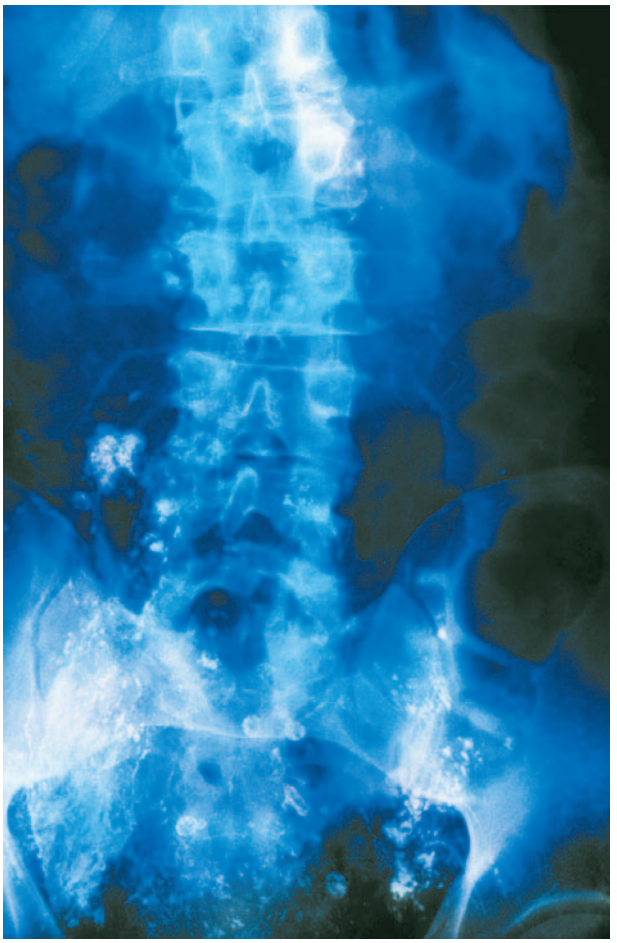
The lymphatic system consists of tissues, organs, and vessels that aid in circulating body fluids and defending the body from damage by foreign substances such as viruses, bacteria, or fungi. However, certain cancers may also spread through the lymphatic system. Thus, lymphangiography is sometimes used to:

- diagnose the presence or spread of tumors, lymphatic cancer (lymphoma), and other cancers

- distinguish primary lymphedema (when swelling in the lymphatic system arises from missing or impaired lymphatic vessels) from secondary lymphedema (swelling caused by damaged lymph vessels or lymph nodes that have been removed)
- localize tumors for surgical removal
- assess the effectiveness of **chemotherapy** and **radiation therapy** in treating problems associated with metastatic (spreading) cancer

Although the results of lymphangiography are considered reliable, additional tests, studies, and clinical observations are necessary to determine a precise diagnosis. By itself, lymphangiography misses cancer in about 20% of cases. One of the major drawbacks of lymphangiography is its failure to fill certain lymphatic channels and groups of lymph nodes—a failure that may be due to infection, injury, or tumor spread. When this filling failure occurs, certain segments of the lymphatic system in the abdomen and pelvis cannot be visualized; thus, metastatic disease can be neither confirmed nor ruled out.

Since the late 1990s, conventional lymphangiography (using an iodine oil-based contrast agent) has been used almost exclusively for the staging of urologic pelvic and testicular malignancies. The test may demonstrate metastases within lymph nodes of normal size that are missed on computed tomography (CT) imaging. Technical innovations in nuclear diagnostics and computer imaging largely replaced lymphangiography with simpler, safer, and more reliable techniques of visualizing the lymphatic system (such as lymphangioscintigraphy, or isotope lymphography).



False-color lymphangiogram of the abdomen of a person suffering from lymphoma. *(Copyright Mehau Kulyk, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Precautions

Because of the possibility of an adverse reaction to the contrast medium, lymphangiography is usually not administered to patients with lung problems, heart disease, or severe kidney or liver disease.

Individuals with allergies to shellfish, iodine, or dye used in other diagnostic tests may receive steroids or antihistamines before the test to decrease the risk of allergic reactions.

Description

Lymphangiography testing may be done on an inpatient or outpatient basis. A sedative may be given to help the patient relax. After the skin of each foot is cleaned with an antiseptic, a blue indicator dye (which does not show up on x rays) is injected between the first, second, and third toes of each foot. The dye spreads into the lymphatic system in about 15 to 30 minutes. The thin, bluish lines that appear on the top of each foot delineate the lymphatic vessels. Next, a local anesthetic is injected, and a small incision is made into one of the larger blue lines in each foot. A needle or catheter (a thin flexible tube) is inserted into a vessel in each foot, and an oil-based contrast medium (such as Ethiodol) is injected at a slow, steady rate. A feeling of pressure may occur as the contrast medium is injected, but the patient must lie still to avoid dislodging the needle.

A fluoroscope (a device consisting of a fluorescent screen on which the shadows of objects that come between the screen and an attached x-ray apparatus can be viewed) is used to monitor the progress of the contrast medium as it spreads slowly (taking about 60 to 90 minutes) through the lymphatic system, traveling up the legs, into the groin, and along the back of the abdominal cavity. After the contrast agent is injected, the catheter is removed and the incisions are stitched and bandaged. Then x rays are taken of the legs, pelvis, abdomen, and chest areas. The following day, an additional set of x rays is obtained.

KEY TERMS

Contrast medium—A substance that provides a contrast between the tissue or organ being filmed and the medium.

Lymph node—A rounded, encapsulated body consisting of an accumulation of lymphatic tissue; found in lymphatic vessels.

Lymphoma—A type of lymphatic cancer.

Metastases—Cancer cells that have spread from the primary site of malignancy to another location in the body.

QUESTIONS TO ASK THE DOCTOR

- What is the purpose of the test?
- How long will the test take?
- Will I be sedated or get anesthesia before the test?
- Is there anything special I need to do before the test?
- Can I drive myself home after testing?
- When will I get the results?

After the test, the patient's skin, feces, and urine may have a bluish tint for two to three days (until the marker dye disappears), and there may be some discomfort behind the knees and in the groin area. Test results are reported to the doctor or patient from a few hours to a few days after the procedure.

Preparation

There is usually no special preparation needed before lymphangiography—such as restrictions in diet, activity, or medication intake. However, some facilities may require a clear liquid diet for a specified period of time before the test. In addition, for comfort reasons, patients may be asked to empty their bladders before testing. A patient undergoing lymphangiography (or a close family member) must sign a consent form before the test is administered.

Aftercare

After testing, the patient's blood pressure, pulse, breathing status, and temperature are monitored at regular intervals until they are stable. Any lung complications are noted, such as hoarseness or shortness of breath, chest pain, low blood pressure, low-grade **fever**, and blueness of lips and nailbeds due to clotting of the dye.

Bedrest for at least 24 hours following the test is recommended, with feet elevated to help reduce swelling at the incision sites. The incision sites may be sore for several days, and ice packs may be applied to these sites to further reduce swelling. The patient should also inspect the incision sites for infection. Sterile dressings should remain in place for two days, and the incision sites should be kept dry until after the sutures are removed (7 to 10 days after the test).

Risks

There is a risk of infection or bleeding caused by introducing the needle or tube through the skin or an allergic reaction—usually not serious— to the contrast medium. There is also a slight risk of oil embolism (obstruction of a blood vessel) due to the oil-based contrast medium. The contrast medium eventually seeps from the lymphatic channels into the general circulation, where it may travel to, and lodge in, the lungs.

There is some radiation exposure involved in the procedure. Although pregnant women and children are particularly sensitive to these risks, physicians may order the procedure when the benefits appear to outweigh the risks.

Normal results

Normal test results indicate no anatomical or functional abnormalities.

Abnormal results

Abnormal results may indicate:

- filariasis (a tropical disease caused by worms living in the lymphatic system)
- Hodgkin's or non-Hodgkin's lymphoma (cancers of the lymphatic system)
- inflammation
- metastatic cancer
- primary lymphedema
- retroperitoneal tumors (tumors lying outside of the peritoneum—the membrane lining the abdominal cavity)
- trauma

Resources

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ORGANIZATIONS

American College of Radiology. <http://www.acr.org>.

Lymphoma Research Foundation of America. <http://www.lymphomafocus.org>.

Genevieve Slomski, Ph.D.

Lymphocyte immune globulin

Definition

Lymphocyte **immune globulin** is a drug used to suppress the immune system. Lymphocyte immune globulin is also known by the generic name anti-thymocyte globulin (ATG) and the brand names Atgam and Thymoglobulin. Atgam first received FDA approval in 1981 and Thymoglobulin in 1999. As of 2001, no generic preparations are available.

Purpose

Lymphocyte immune globulin is used to treat aplastic anemia and to prevent rejections during **bone marrow transplantation**. This drug has also been used experimentally to treat advanced **non-Hodgkin's lymphomas** and cutaneous T-cell lymphomas.

Description

This drug suppresses the immune system by slowing down T cells, cells critical in immunity. Without them, the immune system is essentially paralyzed. Lymphocyte immune globulin contains antibodies that attach to T cells and prevent them from working properly. This drug also decreases the number of T cells in the blood.

Lymphocyte immune globulin is made by vaccinating an animal with immature human T cells, then collecting the antibodies made against them. Atgam is made in horses and Thymoglobulin in rabbits.

Atgam is labeled for use only in kidney transplantation and aplastic anemia, and Thymoglobulin is specifically approved only for kidney transplantation. The effectiveness of either drug for treating aplastic anemia in cancer patients, however, is unknown.

Lymphocyte immune globulin is often used off-label to treat graft-versus-host disease (GVHD) after bone marrow transplantation. The drug has been beneficial for GVHD patients in some studies, but its effectiveness has not been conclusively demonstrated. In some **clinical trials**, it is also being used to prepare the patient's body for bone marrow transplantation. This drug produces short partial remissions of some lymphomas in published experiments.

Recommended dosage

The usual dose of Atgam in adults is 10–30 mg/kg (1 kilogram is 2.2 pounds). Doses of 5–25 mg/kg have been given to a few children. Thymoglobulin, which is about 10 times stronger, has a recommended dose of 1–1.5 mg/kg in adults. Typically these drugs are given daily or every other day for several days or weeks. They are injected into the blood over several hours, under close supervision in the hospital or clinic.

Precautions

Patients should not take Atgam if they are allergic to horse proteins or Thymoglobulin if they are allergic to rabbit proteins. Patients should tell their doctors about any current or previous blood cell problems and about all their prescription and over-the-counter drugs.

Lymphocyte immune globulin can make infections more serious. Patients should check with their doctors if they have any symptoms of an infection, such as chills, **fever**, or sore throat. They should also avoid people with contagious diseases and anyone recently vaccinated with an oral polio vaccine. The drug decreases the effectiveness of vaccinations given just before or during treatment. Some types of **vaccines** are not safe to receive while taking this drug.

Lymphocyte immune globulin does not interact with any specific foods. However, patients should check with their doctor for specific recommendations for eating and drinking before the treatment.

Patients should be careful in planning their activities, as this drug can cause dizziness.

Side effects

Thymoglobulin and Atgam have very similar side effects. However, Thymoglobulin is approximately twice as likely to decrease the number of white blood cells and three times as likely to result in malaise. Dizziness is much more common with Atgam. Other numerous side effects caused by both drugs include:

- Chills or fever in most patients
- Risk of developing an infection, which has been seen in up to 30% of patients, and sepsis in approximately 10%
- Risk of bleeding, due to **thrombocytopenia** (seen in 30–45% of patients)
- Rarely, anemia or the destruction of white blood cells other than T cells
- Pain, swelling, and redness where the drug is injected (minimized by injecting the drug into the faster-moving blood in a large vein)
- Allergic reactions (Serious allergic reactions can cause difficulty breathing, swelling of the tongue, a drop in blood pressure, or pain in the chest, sides, or back. Severe allergic reactions are potentially life-threatening, but rare; milder allergic reactions can result in **itching**, hives, or rash. Skin tests are often done to predict the likelihood of an allergic reaction, but are not foolproof.)
- Serum sickness, an immune reaction against the drug (Can result in fever, chills, muscle and joint aches, rash, blurred vision, swollen lymph nodes, or kidney problems; serum sickness is common when lymphocyte immune globulin is used alone for aplastic anemia, but fairly rare when it is combined with other drugs that suppress immunity.)
- Headaches, pain in the abdomen, **diarrhea**, nausea or vomiting, fluid retention, weakness, rapid heartbeats, or an abnormal increase in blood potassium (these side effects develop in more than a fifth of all patients during treatment)
- Uncommon side effects such as kidney damage, high blood pressure, heart failure, lethargy, abnormal sensations such as prickling in the skin, seizures, pulmonary edema, and adult respiratory distress syndrome
- Risk of developing **lymphoma** or leukemia, if the immune system is greatly suppressed for a long time

Side effects in pregnant or nursing women

The effects of this drug on an unborn child are unknown. Doctors are not sure if this drug reaches breast milk.

KEY TERMS

Adult respiratory distress syndrome (ARDS)—A lung disease characterized by widespread lung abnormalities, fluid in the lungs, shortness of breath, and low oxygen levels in the blood.

Antibodies—Proteins made by the immune system that attach to targeted molecules and cells.

Aplastic anemia—Failure of the bone marrow to make enough blood cells.

Blood cells—Cells found in the blood, including red blood cells that carry oxygen, white blood cells that fight infections, and platelets that help the blood to clot.

Bone marrow—A group of cells and molecules found in the centers of some bones. It makes all of the cells found in the blood, including the cells involved in immunity.

Graft-vs-host disease (GVHD)—A disease that develops when immune cells in transplanted bone marrow attack the body.

Immune system—The cells and organs that defend the body against infections.

Pulmonary edema—A disease characterized by excessive fluid in the lungs and difficulty breathing.

Sepsis—An infection that has spread into the blood.

Serum sickness—A type of allergic reaction against blood proteins. Serum sickness develops when the immune system makes antibodies against proteins that are not normally found in the body.

Skin test—A test used to diagnose allergies.

T lymphocyte or T cell—A type of white blood cell. Helper T cells aid other cells of the immune system, while cytotoxic T cells destroy abnormal body cells, including those that have been infected by a virus.

Thrombocytopenia—Too few platelets in the blood.

Methods of preventing or reducing side effects

Drugs such as antihistamines, acetaminophen, and **corticosteroids** can prevent or decrease some side effects, including fevers, chills, and allergic reactions. **Antibiotics** may help to prevent infections.

Interactions

Combining this drug with other medications that suppress the immune system (including **chemotherapy**) can severely suppress immunity. Drugs that slow blood clotting, such as aspirin, can increase the risk of bleeding. Any drug that reduces the symptoms of an infection, including aspirin and acetaminophen, can increase the risk that a serious infection will go undetected.

See also Myelosuppression; Immune response; Infection and sepsis; Neuropathy.

Anna Rovid Spickler, D.V.M., Ph.D.

Lymphoma

Definition

Lymphoma is the name of a diverse group of cancers of the lymphatic system, a connecting network of glands, organs and vessels whose principle cell is the lymphocyte.

Description

When lymphoma occurs, cells in the lymphatic system grow abnormally. They divide too rapidly and grow without any order or control. Too much tissue is formed and tumors begin to grow. Because there is lymph tissue in many parts of the body, the cancer cells may involve the liver, spleen, or bone marrow.

Two general types of lymphoma are commonly recognized: **Hodgkin's disease** or Hodgkin's lymphoma (HD), and Non-Hodgkin's lymphoma (NHL). The two are distinguished by cell type. These differ significantly in respect of their natural histories and their response to therapy. Hodgkin's disease tends to be primarily of nodal origin. **Non-Hodgkin's lymphomas**, unlike HD, can spread beyond the lymphatic system.

See also AIDS-related cancers.

Kate Kretschmann.

M

Magnetic resonance imaging

Definition

Magnetic resonance imaging (MRI) is one of the newest, and perhaps most versatile, medical imaging technology available. Doctors can get highly refined images of the body's interior without surgery using MRI. By using strong magnets and pulses of radio waves to manipulate the natural magnetic properties in the body, this technique makes better images of organs and soft tissues than those of other brain scanning technologies. MRI is particularly useful for imaging the brain and spine, as well as the soft tissues of joints and the interior structure of bones, as well as the liver. The entire body is visible with MRI, and the technique poses few known health risks.

Purpose

MRI was developed in the 1980s. Its technology has been developed for use in magnetic resonance **angiography** (MRA), magnetic resonance spectroscopy (MRS), and, more recently, magnetic resonance cholangiopancreatography (MRCP). MRA was developed to study blood flow, whereas MRS can identify the chemical composition of diseased tissue and produce color images of brain function. MRCP is evolving into a potential noninvasive alternative for the diagnostic procedure **endoscopic retrograde cholangiopancreatography** (ERCP).

Advantages

DETAIL MRI creates precise images of the body based on the varying proportions of magnetic elements in different tissues. Very minor fluctuations in chemical composition can be determined. MRI images have greater natural contrast than standard x rays, computed tomography scan (CT scan), or ultrasound, all of which depend on the differing physical properties of tissues. This sensitivity allows MRI to distinguish fine variations in tissues deep within the body. It is also particularly useful for spotting and distinguishing diseased tissues (tumors and other lesions) early in their development. Often, doctors prescribe an MRI scan to more fully investigate earlier findings of other imaging techniques.

SCOPE The entire body can be scanned, from head to toe and from the skin to the deepest recesses of the brain. Moreover, MRI scans are not obstructed by bone, gas, or body waste, which can hinder other imaging techniques. (Although the scans can be degraded by motion such as breathing, heartbeat, and bowel activity.) The MRI process produces cross-sectional images of the body that are as sharp in the middle as on the edges, even of the brain through the skull. A close series of these two-dimensional images can provide a three-dimensional view of the targeted area. Along with images from the cross-sectional plane, the MRI can also provide images sagitally (from one side of the body to the other, from left to right for example), allowing for a better three-dimensional interpretation, which is sometimes very important for planning a surgical approach.

SAFETY MRI does not depend on potentially harmful ionizing radiation, as do standard **x ray** and computer tomography scans. There are no known risks specific to the procedure, other than for people who might have metal objects in their bodies.

Despite its many advantages, MRI is not routinely used because it is a somewhat complex and costly procedure. MRI requires large, expensive, and complicated equipment; a highly trained operator; and a doctor specializing in radiology. Generally, MRI is prescribed only when serious symptoms or negative results from other tests indicate a need. Many times another test is appropriate for the type of diagnosis needed.

Uses

Doctors may prescribe an MRI scan of different areas of the body.

BRAIN AND HEAD MRI technology was developed because of the need for brain imaging. It is one of the few imaging tools that can see through bone (the skull)

and deliver high quality pictures of the brain's delicate soft tissue structures. MRI may be needed for patients with symptoms of a brain tumor, stroke, or infection (like meningitis). MRI may also be needed when cognitive or psychological symptoms suggest brain disease (like Alzheimer's or Huntington's diseases, or multiple sclerosis), or when developmental retardation suggests a birth defect. MRI can also provide pictures of the sinuses and other areas of the head beneath the face. In adult and pediatric patients, MRI may be better able to detect abnormalities than compared to computed tomography scanning.

SPINE Spinal problems can create a host of seemingly unrelated symptoms. MRI is particularly useful for identifying and evaluating degenerated or herniated spinal discs. It can also be used to determine the condition of nerve tissue within the spinal cord.

JOINT MRI scanning is most commonly used to diagnose and assess joint problems. MRI can provide clear images of the bone, cartilage, ligament, and tendon that comprise a joint. MRI can be used to diagnose joint injuries due to sports, advancing age, or arthritis. MRI can also be used to diagnose shoulder problems, such as a torn rotator cuff. MRI can also detect the presence of an otherwise hidden tumor or infection in a joint, and can be used to diagnose the nature of developmental joint abnormalities in children.

SKELETON The properties of MRI that allow it to see through the skull also allow it to view the inside of bones. Accordingly, it can be used to detect bone cancer, inspect the marrow for leukemia and other diseases, assess bone loss (osteoporosis), and examine complex fractures.

HEART AND CIRCULATION MRI technology can be used to evaluate the circulatory system. The heart and blood flow provides a good natural contrast medium that allows structures of the heart to be clearly distinguished.

THE REST OF THE BODY Whereas computed tomography and ultrasound scans satisfy most chest, abdominal, and general body imaging needs, MRI may be needed in certain circumstances to provide better pictures or when repeated scanning is required. The progress of some therapies, like liver cancer therapy, needs to be monitored, and the effect of repeated x-ray exposure is a concern.

Precautions

MRI scans and metal

MRI scanning should not be used when there is the potential for an interaction between the strong MRI magnet and metal objects that might be imbedded in a patient's body. The force of magnetic attraction on certain types of metal objects (including surgical steel) could move them within the body and cause serious injury. Metal may be imbedded in a person's body for several reasons.

MEDICAL People with implanted cardiac pacemakers, metal aneurysm clips, or who have broken bones repaired with metal pins, screws, rods, or plates must tell their radiologist prior to having an MRI scan. In some cases (like a metal rod in a reconstructed leg), the difficulty may be overcome.

INJURY Patients must tell their doctors if they have bullet fragments or other metal pieces in their body from old wounds. The suspected presence of metal, whether from an old or recent wound, should be confirmed before scanning.

OCCUPATIONAL People with significant work exposure to metal particles (e.g., working with a metal grinder) should discuss this with their doctors and radiologists. The patient may need prescan testing—usually a single, regular x ray of the eyes to see if any metal is present.

Chemical agents

Chemical agents designed to improve the picture or allow for the imaging of blood or other fluid flow during MRA may be injected. In rare cases, patients may be allergic to, or intolerant of, these agents, and these patients should not receive them. If these chemical agents are to be used, patients should discuss any concerns they have with their doctor and radiologist.

Side effects

The potential side effects of magnetic and electric fields on human health remain a source of debate. In particular, the possible effects on an unborn baby are not well known. Any woman who is, or may be, pregnant, should carefully discuss this issue with her doctor and radiologist before undergoing a scan.

As with all medical imaging techniques, obesity greatly interferes with the quality of MRI.

Description

In essence, MRI produces a map of hydrogen distribution in the body. Hydrogen is the simplest element known, the most abundant in biological tissue, and one that can be magnetized. It will align itself within a strong magnetic field, like the needle of a compass. The earth's magnetic field is not strong enough to keep a person's hydrogen atoms pointing in the same direction, but the

superconducting magnet of an MRI machine can. This comprises the magnetic part of MRI.

Once a patient's hydrogen atoms have been aligned in the magnet, pulses of very specific radio wave frequencies are used to knock them back out of alignment. The hydrogen atoms alternately absorb and emit radio wave energy, vibrating back and forth between their resting (magnetized) state and their agitated (radio pulse) state. This comprises the resonance part of MRI.

The MRI equipment records the duration, strength, and source location of the signals emitted by the atoms as they relax and translates the data into an image on a television monitor. The state of hydrogen in diseased tissue differs from healthy tissue of the same type, making MRI particularly good at identifying tumors and other lesions. In some cases, chemical agents such as gadolinium can be injected to improve the contrast between healthy and diseased tissue.

A single MRI exposure produces a two-dimensional image of a slice through the entire target area. A series of these image slices closely spaced (usually less than half an inch) makes a virtual three-dimensional view of the area.

Magnetic resonance spectroscopy (MRS) is different from MRI because MRS uses a continuous band of radio wave frequencies to excite hydrogen atoms in a variety of chemical compounds other than water. These compounds absorb and emit radio energy at characteristic frequencies, or spectra, which can be used to identify them. Generally, a color image is created by assigning a color to each distinctive spectral emission. This comprises the spectroscopy part of MRS. MRS is still experimental and is available only in a few research centers.

Doctors primarily use MRS to study the brain and disorders like epilepsy, Alzheimer's disease, brain tumors, and the effects of drugs on brain growth and metabolism. The technique is also useful in evaluating metabolic disorders of the muscles and nervous system.

Magnetic resonance angiography (MRA) is another variation on standard MRI. MRA, like other types of angiography, looks specifically at fluid flow within the blood (vascular) system, but does so without the injection of dyes or radioactive tracers. Standard MRI cannot make a good picture of flowing blood, but MRA uses specific radio pulse sequences to capture usable signals.

The technique is generally used in combination with MRI to obtain images that show both vascular structure and flow within the brain and head in cases of stroke, or when a blood clot or aneurysm is suspected.

MRI technology is also being applied in the evaluation of the pancreatic and biliary ducts in a new study called magnetic resonance cholangiopancreatography (MRCP). MRCP produces images similar to that of endoscopic retrograde cholangiopancreatography (ERCP), but in a non-invasive manner. Because MRCP is new and still very expensive, it is not readily available in most hospitals and imaging centers.

Regardless of the exact type of MRI planned, or area of the body targeted, the procedure involved is basically the same. In a special MRI suite, the patient lies down on a narrow table and is made as comfortable as possible. Transmitters are positioned on the body and the table moves into a long tube that houses the magnet. The tube is as long as an average adult lying down, and is open at both ends. Once the area to be examined has been properly positioned, a radio pulse is applied. Then a two-dimensional image corresponding to one slice through the area is made. The table then moves a fraction of an inch and the next image is made. Each image exposure takes several seconds and the entire exam will last anywhere from 30 to 90 minutes. During this time, the patient must remain still as movement can distort the pictures produced.

Depending on the area to be imaged, the radio-wave transmitters will be positioned in different locations.

- For the head and neck, a helmet-like covering is worn on the head.
- For the spine, chest, and abdomen, the patient will be lying on the transmitters.
- For the knee, shoulder, or other joint, the transmitters will be applied directly to the joint.

Additional probes will monitor vital signs (like pulse, respiration, etc.) throughout the test.

The procedure is somewhat noisy and can feel confining to many patients. As the patient moves through the tube, the patient hears a thumping sound. Sometimes, music is supplied via earphones to drown out the noise. Some patients may become anxious or feel claustrophobic while in the small, enclosed tube. Patients may be reassured to know that throughout the study, they can communicate with medical personnel through an intercom-like system.

Recently, open MRIs have become available. Instead of a tube open only at the ends, an open MRI also has opening at the sides. Open MRIs are preferable for patients who have a fear of closed spaces and become anxious in traditional MRI machines. Open MRIs can also better accommodate obese patients, and allow parents to accompany their children during testing.

If the chest or abdomen is to be imaged, the patient will be asked to hold his to her breath as each exposure is made. Other instructions may be given to the patient as needed. In many cases, the entire examination will be performed by an MRI operator who is not a doctor. However, the supervising radiologist should be available to consult as necessary during the exam, and will view and interpret the results sometime later.

Preparation

In some cases (such as for MRI brain scanning or MRA), a chemical designed to increase image contrast may be given immediately before the exam. If a patient suffers from anxiety or claustrophobia, drugs may be given to help the patient relax.

The patient must remove all metal objects (watches, jewelry, eye glasses, hair clips, etc.). Any magnetized objects (like credit and bank machine cards, audio tapes, etc.) should be kept far away from the MRI equipment because they can be erased. The patient cannot bring any personal items such as a wallet or keys into the MRI machine. The patient may be asked to wear clothing without metal snaps, buckles, or zippers, unless a medical gown is worn during the procedure. The patient may be asked not to use hair spray, hair gel, or cosmetics that could interfere with the scan.

Aftercare

No aftercare is necessary, unless the patient received medication or had a reaction to a contrast agent. Normally, patients can immediately return to their daily activities. If the exam reveals a serious condition that requires more testing or treatment, appropriate information and counseling will be needed.

Risks

MRI poses no known health risks to the patient and produces no physical side effects. Again, the potential effects of MRI on an unborn baby are not well known. Any woman who is, or may be, pregnant, should carefully discuss this issue with her doctor and radiologist before undergoing a scan.

Normal results

A normal MRI, MRA, MRS, or MRCP result is one that shows the patient's physical condition to fall within normal ranges for the target area scanned.

KEY TERMS

Angiography—Any of the different methods for investigating the condition of blood vessels, usually via a combination of radiological imaging and injections of chemical tracing and contrast agents.

Gadolinium—A very rare metallic element useful for its sensitivity to electromagnetic resonance, among other things. Traces of it can be injected into the body to enhance the MRI pictures.

Hydrogen—The simplest, most common element known in the universe. It is composed of a single electron (negatively charged particle). It is the nuclear proton of hydrogen that makes MRI possible by reacting resonantly to radio waves while aligned in a magnetic field.

Ionizing radiation—Electromagnetic radiation that can damage living tissue by disrupting and destroying individual cells. All types of nuclear decay radiation (including x rays) are potentially ionizing. Radio waves do not damage organic tissues they pass through.

Magnetic field—the three-dimensional area surrounding a magnet, in which its force is active. During MRI, the patient's body is permeated by the force field of a superconducting magnet.

Radio waves—Electromagnetic energy of the frequency range corresponding to that used in radio communications, usually 10,000 cycles per second to 300 billion cycles per second. Radio waves are the same as visible light, x rays, and all other types of electromagnetic radiation, but are of a higher frequency.

Abnormal results

Generally, MRI is prescribed only when serious symptoms or negative results from other tests indicate a need. There often exists strong evidence of a condition that the scan is designed to detect and assess. Thus, the results will often be abnormal, confirming the earlier diagnosis. At that point, further testing and appropriate medical treatment is needed. For example, if the MRI indicates the presence of a brain tumor, an MRS may be prescribed to determine the type of tumor so that aggressive treatment can begin immediately without the need for a surgical biospy.

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Kurt Richard Sternlof

Male breast cancer

Definition

Male **breast cancer** is a malignant tumor that forms in a man's breast.

Description

Breast cancer is rare in men, but can be serious and fatal. Many people believe that only women can get breast cancer, but men have breast tissue that also can develop cancer. When men and women are born, they have a small amount of breast tissue with a few tubular passages called ducts located under the nipple and the area around the nipple (areola). By puberty, female sex hormones cause breast ducts to grow and milk glands to form at the ends of the ducts. But male hormones eventually prevent further breast tissue growth. Although male breast tissue still contains some ducts, it will have only a few—or no—lobules. Near the breasts of men and women are axillary lymph nodes. These are underarm small structures shaped like beans that collect cells from lymphatic vessels. Lymphatic vessels carry lymph, a clear fluid that contains fluid from tissues, cells from the immune system, and various waste products throughout the body. The axillary lymph nodes are important to breast cancer patients, as they play a role in the spread and staging of breast cancer.

Breast cancer is much more common in women, mostly because women have many more breast cells that can undergo cancerous changes and because women are exposed to the effects of female hormones.

Infiltrating ductal **carcinoma** is the most common type of breast cancer in men. It is a type of **adenocarcinoma**, or a type of cancer that occurs in glandular tissue. Infiltrating ductal carcinoma starts in a breast duct and spreads beyond the cells lining the ducts to other tissues in the breast. Once the cancer begins spreading into the breast, it can spread to other parts of the body. This distant spread is called **metastasis**. When breast cancer metastasizes to other areas of the body, it can cause serious, life-threatening consequences. For example, breast cancer might spread to the liver or lungs. About 80% to 90% of all male breast cancers are infiltrating ductal carcinomas.

Ductal carcinoma in situ (DCIS) is not common; it accounts for about 10% of all male breast cancers. It also is an adenocarcinoma. In situ cancers remain in the immediate area where they began, so DCIS remains confined to the breast ducts and does not spread to the fatty tissues of the breast. This means it is likely found early. DCIS also may be called intraductal carcinoma.

Other types of breast cancer are very rare in men. Adenocarcinomas that are lobular (forming in the milk glands or lobules) only occur in about 2% of male breast cancer cases because men normally do not have milk gland tissues. Inflammatory breast cancer, a serious form of breast cancer in which the breast looks red and swollen and feels warm, also occurs rarely. Paget's disease of the nipple, a type of breast cancer that grows from the ducts beneath the nipple onto the nipple's surface, only accounts for about 1% of female breast cancers. However, slightly more men have this form of breast cancer than women. Sometimes, Paget's disease is associated with another form of breast cancer.

Although not a form of cancer, but a benign condition, gynecomastia is important to mention. It is the most common of all male breast disorders and can be associated with male breast cancer in a rare condition called Klilnefelter's syndrome. Gynecomastia most often occurs in teenage boys when their hormones change during puberty. Older men also may experience the condition when their hormone balance changes as they age. Gynecomastia is an increase in the amount of breast tissue, or breast tissue enlargement. If a man has Klinefelter's syndrome, he can develop gynecomastia and increased risk of breast cancer.

Demographics

Breast cancer in men is rare, accounting for less than 1% of all breast cancers. Still, about 1,450 American men were diagnosed with the disease and 470 men died from it in 2004. Although studies show the number of breast cancer cases in women has decreased in the United States and Europe since the 1960s, the number of breast cancer cases in men have not decreased, but remained stable or slightly increased.

The rate of increase in cases begins and steadily rises at age 50 for men. However, the average age for male breast cancer is between 60 and 70 years old, with a median age of 67 years. Men often are diagnosed at a later stage than women.

Causes and symptoms

Scientists do not know what causes most cases of male breast cancer. However, excellent progress is being made in genetic research and in understanding how genes instruct cells to grow, divide, and die. For example, researchers have now mapped all of the genes in the human body. Genes are part of the body's DNA, which is the chemical that instructs the cells. When DNA or genes carry defects (mutations), they activate changes in the cells, such as rapid cell division, that lead to cancer. Some genes, called tumor suppression genes, cause cells to die. Scientists have identified some genetic mutations that are risk factors for breast cancer. In other cases, environmental, or outside, factors are thought to increase a man's risk for breast cancer.

Mutations of at least two versions of a tumor suppressor gene (BRCA1 and BRCA2) have been identified as causes of breast cancer in women. In men, the BRCA2 mutation is considered responsible for about 15% of breast cancers. Men can inherit genes from either parent. Studies have shown that BRCA1 also may increase a man's risk for breast cancer, but its role is less certain. These mutations have been shown to increase other cancers in men, including **prostate cancer**. Klinefelter's syndrome is a rare genetic cause of breast cancer in men. It results from inheriting an additional X chromosome.

Several other factors also may cause male breast cancer. Some conditions, such as the liver disease cirrhosis, can cause an imbalance in a man's hormones, producing high levels of the female hormone estrogen, which can lead to breast cancer. Exposure to some substances such as high amounts of radiation may contribute to male breast cancer. A 2004 report studied why a cluster of breast cancer cases occurred among a small group of men who worked in the basement office of a multi-story office building. The study linked their breast cancer to exposure to high magnetic fields from a nearby electrical switchgear room in their work space.

Many men do not realize they can develop breast cancer; they ignore the symptoms. The most common symptom is a mass, or lump in the chest area, particularly around the nipple. The lump will be firm, not tender or

painful. Other signs that may warn of male breast cancer include:

- Skin dimpling or puckering
- Changes in the nipple, such as drawing inward (retraction)
- Nipple discharge of any kind
- Redness or scaling of the nipple or breast skin
- Abnormal swelling (or lump) of the breast, nipple, or chest muscle
- Prolonged rash or irritation of the nipple, which may indicate Paget's disease

Diagnosis

Physicians follow the same steps for diagnosing breast cancer in men as in women, except that routine screening of breast cancer is not done in men. Once symptoms are noticed, however, physicians will proceed in the same way. The physician will conduct a thorough medical history and examination, including questions that may identify risk factors for breast cancer, such as male or female relatives with the disease. The medical history also helps gather details on possible symptoms for breast cancer.

The physician also performs a clinical breast examination. This helps locate and study a lump or suspicious area. The physician will feel (palpate) a mass to get an idea of its size, texture, likely location and relation to surrounding skin, muscles and tissues. At this point, the physician already will begin to look for signs that the cancer may have spread to other organs and to the lymph nodes. The physician will palpate lymph nodes and the liver, for instance, to see if they are enlarged.

The next step in diagnosis usually is a diagnostic mammogram. **Mammography** is an x ray of the breast. Mammograms are performed by radiologic technologists who take special training in the procedure. Mammograms are evaluated by radiologists, physicians who receive medical training specifically in interpreting **x rays**. If the initial mammogram shows suspicious findings, the radiologist may order magnification views to more closely look at the suspicious area. Mammograms can accurately show the tissue in the breast, even more so in men than women, because men do not have dense breasts or benign cysts in their breasts that interfere with the diagnosis.

The radiologist also might recommend an ultrasound to follow up on suspicious findings. Ultrasound often is used to image the breasts. Also known as sonography, the technique uses high-frequency sound waves to take pictures of organs and functions in the body. Sound wave echoes can be converted by computer to an image and displayed on a computer screen. Ultrasound does not use radiation. A technologist will perform the ultrasound; it will be evaluated by the radiologist.

Biopsies, which involve removing a sample of tissue, are the only definite way to tell if a mass is cancerous. At one time, surgical biopsies were the only option, requiring removal of all or a large portion of the lump in a more complicated procedure. Today, fine-needle aspiration **biopsy** and core biopsies can be performed. In fine-needle aspiration biopsy, a thin needle is inserted to withdraw fluid from the mass. The physician may use ultrasound or other imaging guidance to locate the mass if necessary. The fluid is tested in a laboratory under a special microscope to determine if it is cancerous.

A core biopsy is similar, but involves removing a small cylinder of tissue from the mass through a slightly larger needle. Core biopsy may require local anesthesia. These biopsy techniques usually can be performed in a physician office or outpatient facility. The cells in biopsy samples help physicians determine if the lump is cancerous and the type of breast cancer. A tissue sample also may be used for assigning a grade to the cancer and to test for certain proteins and receptors that aid in treatment and prognosis decisions.

If there is discharge from the nipple, the fluid also may be collected and analyzed in a laboratory to see if cancer cells are present in the fluid.

Diagnosis of breast cancer spread may require additional tests. For example, a **computed tomography** (CT) scan may be ordered to check organs such as the liver or kidney for possible metastasized cancer. A chest x ray can initially check for cancer spread to the lungs. Bone scans are nuclear medicine procedures that look for areas of diseased bone. **Magnetic resonance imaging** (MRI) has been increasingly used in recent years as a follow-up study to mammograms when findings are not clear. However, for metastatic breast cancer, they are more likely to be ordered to check for cancer in the brain and spinal cord. **Positron emission tomography** (PET) scans also have become more common in recent years.

Treatment team

The treatment team for male breast cancer normally consists of a primary care physician, a medical oncologist (cancer specialist) and if **radiation therapy** is used, a radiation oncologist. Many other staff also are involved. For instance, special oncology nurses help

guide patients through their care and recovery. Radiation therapists are specially trained technologists who deliver the radiation therapy treatments prescribed by the radiation oncologist.

Clinical staging, treatments, and prognosis

A technique called sentinel **lymph node biopsy** may be the first step in staging. The sentinel node is the first one the cancer cells are likely to reach, so it is the first one checked for cancerous cells. Using a radioactive substance and blue dye injected into the area around the tumor, physicians can track the path of the cells and stage the cancer. The technique has been used for many years on women with breast cancer; research in 2004 showed it worked well for predicting lymph node status in men as well.

Staging

Cancer staging systems help physicians compare treatments and research and identify patients for **clinical trials**. Most of all, they help physicians determine treatment and prognosis for individual patients by describing how severe a patient's cancer is in relation to the primary tumor. The most common system used for cancer is the American Join Committee on Cancer (AJCC) TNM system, which bases staging largely on the spread of the cancer. T stands for tumor and describes the tumor's size and spread locally, or within the breast and to nearby organs. The letter N stands for lymph nodes and describes the cancer's possible spread to and within the lymph node system. In some descriptions below, the cancer may have been found by sentinel node biopsy as microscopic disease in nodes that are in the breasts (rather than the armpits). For simplification, these findings have been grouped with the axillary lymph nodes. M stands for metastasis to note if the cancer has spread to distant organs. Further letters and numbers may follow these three letters to describe number of lymph nodes involved, approximate tumor sizes, or other information. The following is a summary of breast cancer stages:

Stage 0: Tis, N0, M0: Ductal carcinoma in situ (DCIS). This is the earliest and least invasive form of breast cancer; the cancer cells are located within a duct and have not invaded surrounding fatty tissue.

Stage I: T1, N0, M0: The tumor is less than 1 in. in diameter (2 cm or less) and has not spread to lymph nodes or distant organs.

Stage IIA: T0, N1, M0/T2, NO, MO: No tumor is found or the tumor is smaller than 2 cm and cancer is found in one to three axillary lymph nodes (even if no tumor is found), or the tumor is between 2 and 5 cm in diameter but has not spread to the axillary lymph nodes. The cancer has not spread to distant organs.

Stage IIIB: T2, N1, M0/T3, NO, MO: The tumor is between 2 and 5 cm in diameter and has spread to one to three axillary lymph nodes or the tumor is larger than 5 cm, has not grown into the chest wall or spread to the lymph nodes or distant organs.

Stage IIIA: T0-2, N2, M0/T3, N1, MO: The tumor is smaller than 5 cm in diameter and has spread to four to nine axillary lymph nodes or the tumor is larger than 5 cm and has spread to one to nine axillary lymph nodes. The cancer has not spread to distant organs.

Stage IIIB: T4, N0-2, M0: The tumor has grown into the chest wall or the skin and may have spread to no lymph nodes or as many as nine lymph nodes. Cancer has not spread to distant sites.

Stage IIIC: T0-4, N3, MO: The tumor is any size, has spread to 10 or more axillary lymph nodes or to one or more lymph nodes under or above the collarbone (clavicle) on the same side as the breast tumor. The cancer has not spread to distant organs.

Inflammatory breast cancer: Classified as stage III, unless it has spread to distant organs or lymph nodes not near the breast (which would classify it as Stage IV).

Stage IV: T0-4, N0-3, M1: Regardless of the tumor's size, the cancer has spread to distant organs, such as the liver, bones, or lung, or to lymph nodes far from the breast.

Treatment

If the axillary lymph nodes were identified as containing cancer at the time of the sentinel lymph node biopsy, they will be removed in an axillary dissection. Sometimes, this is done at the time of the biopsy.

For Stage I, surgery often is the only treatment needed for men. Women often have lumpectomies, which remove as little surrounding breast tissue as possible, to preserve some of their breast shape. For men, this is less of a concern, and **mastectomy**, or surgical removal of the breast, is performed in 80% of all male breast cancers. Men with Stage I tumors larger than 1 cm may receive additional (adjuvant) **chemotherapy**.

Men with Stage II breast cancer also usually receive a mastectomy. If they have cancer in the lymph nodes, they probably will receive adjuvant therapy. Those with estrogen receptor-positive tumors may receive hormone therapy with **tamoxifen**. The treatment team may recommend adjuvant radiation therapy if the cancer has spread to nearby lymph nodes and/or to the skin.

Stage III breast cancer requires mastectomy followed by adjuvant therapy with tamoxifen when hormones are involved. Most patients with Stage III disease also will require chemotherapy and radiation therapy to the chest wall.

Men with Stage IV breast cancer will require systemic therapy, or chemotherapy and perhaps hormonal therapy that works throughout the body to fight the cancer in the breast, as well as the cancer cells that have spread. Patients also may receive immunotherapy to help patients fight infection following chemotherapy. Radiation and surgery also may be used to relieve symptoms of the primary cancer and areas where the cancer may have spread. The treatment team also may have to diagnose specific treatments for the metastatic cancers, depending on their sites.

If male breast cancer recurs in the breast or chest wall, it can be treated with surgical removal and followed by radiation therapy. An exception is recurrence in the same area, where additional radiation therapy can damage normal tissue. Recurrence of the cancer in distant sites is treated the same as metasteses found at the time of diagnosis.

Prognosis

Prognosis for male breast cancer varies, depending on stage. Generally, prognosis is poorer for men than for women, because men tend to show up for diagnosis when their breast cancer has reached a later stage. The average five-year survival rate for Stage I cancers is 96%. For Stage II, it is 84%. Stage III cancers carry an average five-year survival rate of 52%, and by Stage IV, the rate drops to 24%.

Alternative and complementary therapies

Many alternative and complementary therapies can help cancer patients relax and deal with pain, though none to date have been shown to treat or prevent male breast cancer. For example, traditional Chinese medicine offers therapies that stress the importance of balancing energy forces. Many studies also show that guided imagery, prayer, meditation, laughter, and a positive approach to cancer can help promote healing. Early studies have shown that soy and flaxseed may have some preventive properties for breast cancer. However, these trials have been conducted in women. When looking for these therapies, cancer support groups suggest asking for credible referrals and working with the medical treatment team to coordinate alternative and complementary care.

Coping with cancer treatment

It is difficult for some men to accept and cope with a breast cancer diagnosis, since it is a relatively rare and unexpected disease among men. It is important that men work closely with their treatment team to talk about the their concerns and to carefully follow all instructions for care. Support groups and family support are critical in coping with a breast cancer diagnosis.

Eating a nutritious diet, stopping use of tobacco, and limiting use of alcohol, can help in recovery from breast cancer. Beginning a regular exercise program when the treatment team recommends also helps.

KEY TERMS

Lymph node—One of a number of small, bean-shaped structures that run along the lymphatic system of vessels. The lymph nodes trap cancer cells, along with other cells and fluids.

Malignant—Causing worsening or death. Malignant tumors can invade other tissues and organs and spread to other areas of the body.

Clinical trials

Research currently is underway to test various chemotherapy combinations for male breast cancer at different stages. A clinical trial also is underway to investigate a vaccine for treating patients with metastatic breast cancer. The National Institutes of Health list clinical trials by disease type, including those for which they are recruiting patients. Choosing to participate in a clinical trial is a decision that involves the patient, family, and treatment team.

Prevention

Some forms of male breast cancer cannot be prevented. But detecting the cancer at an early stage can prevent serious complications, such as spread to distant organs. Men who have a history of breast cancer in their family should pay particular attention to the symptoms of breast cancer and seek immediate medical evaluation. Physicians may be able to test the blood of men with family history for presence of the BRCA2 gene so they may more carefully watch for early signs of breast cancer. Avoiding exposure to radiation also may help present some male breast cancers.

Special concerns

Men should remember that there are important difference between male and female breast cancers. Some experts say that specific guidelines and instructions for men with breast cancer are noticeably lacking, so men

QUESTIONS TO ASK YOUR DOCTOR

- What type of breast cancer do I have?
- How far has my cancer advanced; what stage is it in?
- What treatments are most appropriate for my type and stage of breast cancer? Which treatment or treatments do you recommend and why?
- How can I prepare for my breast cancer treatment? What side effects can I expect from each treatment?
- Is there anything I can do to keep the cancer from recurring or signs to watch for?

should not be afraid to ask questions or to push a physician for more information when he suspects he might have a suspicious lump or finding in his breast.

Resources

BOOKS

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ORGANIZATIONS

American Cancer Society. 800-ACS-2345. http://www.cancer.org.

The Susan G. Komen Breast Cancer Foundation. 5005 LBJ Freeway, Ste, 250, Dallas, TX 75244. 800-I'M AWARE. http://www.komen.org.

Y-ME National Breast Cancer Organization. 212 W. Van Buren, Ste. 1000, Chicago, IL. 60607-3098. 800-221-2121. http://www.y-me.org.

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Teresa G. Odle

Malignant fibrous histiocytoma

Definition

Malignant fibrous histiocytoma (MFH), although rare, is the most common abnormal growth of soft tissue (sarcoma) in adults.

Description

MFH occurs as a painless mass most commonly in the skin, arms, legs, kidneys, or the pancreas. More rarely MFH may occur in the bones, heart, breasts, or inside the skull.

When MFHs spread (metastasize) to other organs, the most common site is the lung, but **metastasis** to local lymph nodes and to bone have also been reported.

MFHs tend to be slow growing and slow to metastasize.

Local recurrence of MFH after surgery to remove the initial tumor is common because MFHs grow along the fat layers that separate different layers of soft tissue. Often, an MFH is not completely removed because it has crossed, undetected, from one fat layer to another neighboring layer.

Demographics

MFHs are diagnosed in six of every one million people each year. MFHs can occur in people of any age, but they are extremely rare in children.

MFHs occur in a slightly higher frequency in Caucasians than in people of African descent or Asians. No relationship of MFHs appear to exist to any geographic region. Males are affected in slightly higher numbers than are females.

MFHs of the skin are seen almost exclusively in sun-exposed areas of the skin in elderly patients.

People affected with certain genetic diseases, such as neurofibromatosis, have a higher incidence of MFHs than unaffected people.

MFHs of the bone are seen almost exclusively in people who have a pre-existing skeletal disorder such as Paget disease or fibrous dysplasia of bone.

Causes and symptoms

The cause, or causes, of MFHs are not known. An elevated risk for the development of MFHs has been linked to the chemical phenoxyacetic acid found in herbicides; to clorphenols found in wood preservatives; and to exposure to asbestos. People who have been exposed to high doses of radiation are also more prone to develop MFHs than the remainder of the population. Research is ongoing to determine if there is a genetic cause of MFHs.

The only direct symptom of MFHs is the presence of an abnormal mass, but some patients may also experience:

- abnormally high levels of a certain type of white blood cells (eosinophils) in the blood
- low blood sugar (hypoglycemia)
- fever
- abnormal liver function tests

Diagnosis

Prior to removal, MFHs are extremely difficult to distinguish from the other forms of soft tissue sarcoma. The definitive diagnosis of MFH usually occurs after a tumor has been surgically removed. This diagnosis is accomplished by conducting microscopic examinations on the tumor.

Treatment team

Treatment for MFHs is mostly surgical or observational. Surgeries to remove MFHs are generally performed by orthopedic surgeons. MFHs rarely require any chemotherapies or radiation therapies, however, when these treatments are called for they are directed by a medical oncologist and administered by health care personnel who specialize in these fields.

KEY TERMS

Liver function tests (LFTs)—Blood tests that measure the blood serum levels of several enzymes produced by the liver.

Sarcoma—A form of cancer that arises from within the supportive tissues, such as bone, cartilage, fat, or muscle.

Clinical staging, treatments, and prognosis

MFHs are divided into three grades based on the appearance of the tissue within the tumor. Low grade tumors may closely resemble the surrounding normal tissue. Intermediate and high grade tumors may have little resemblance to normal tissue.

Additionally, MFHs are divided into two clinical stages based on size. Stage one MFHs are those tumors that are under 5 centimeters (2 inches) in diameter. Stage two MFHs are those tumors larger than 5 centimeters (2 inches) in diameter.

A treatment plan is determined after the grade and stage of the tumor has been established. High and intermediate grade tumors generally, regardless of the stage, are surgically removed. Low grade, stage one, tumors may be observed for development to a higher grade or stage rather than removed if it is determined that the risks of anesthetic and surgery outweigh the risk of the tumor to the individual patient.

Stage one MFHs are generally removed by wide local excision. This technique involves the surgical removal of the tumor and an area of healthy surrounding tissue that is approximately the same size as the tumor itself.

Stage two MFHs require wide surgical excision with the removal of wider margins of healthy tissue than those margins removed in the excision of smaller tumors. In some instances, stage two MFHs may require **amputation**.

Post-operative treatment of MFH patients may include **chemotherapy** or **radiation therapy**, especially in cases of MFH of the bones and in cases of metastasis to the lungs.

In cases of large MFHs, the patient may undergo radiation treatments prior to surgery in an attempt to shrink the size of the tumor prior to excision.

As of 2000, overall survival from MFH was approximately 75% five-year disease-free survival. The prognosis is generally poorer if:

QUESTIONS TO ASK THE DOCTOR

- Which type of MFH do I have?
- What is the size of my tumor?
- Will I require chemotherapy or radiation treatments to shrink my tumor prior to its removal?
- What is the likelihood of my type of MFH coming back?
- How often should I seek follow-up examinations?

- the disease has metastasized to the lungs or bones
- complete tumor removal is not accomplished, or is not possible
- the patient is of an advanced age
- the tumor is large
- the location of the tumor is somewhere other than the arms or legs
- the tumor is located deep in the body, rather than superficially

Alternative and complementary therapies

There are no effective alternative treatments for MFHs other than surgical removal with or without chemotherapy or radiation treatments.

Coping with cancer treatment

Most patients who undergo wide local excision to remove their tumors can resume their normal activities within a few days of the operation.

The loss of a limb may produce feelings of grief that are similar to that felt upon the death of a spouse or close family member. Patients who must undergo amputation to remove their cancer may require extended psychological care to help them to deal with this grief and to help them develop a new, healthy, **body image**. These patients may also require extended physical therapy to learn to operate without the missing limb or to learn to use a prosthetic device.

Clinical trials

There were 40 **clinical trials** underway, in early 2001, aimed at the treatment of MFHs and other soft tissue **sarcomas**. More information on these trials, including contact information, may be found by conducting a clinical trial search at the website of the National Cancer Institute, CancerNet <http://cancernet.nci.nih.gov/trialsrch.shtml>.

Prevention

Because the causes of MFHs are not known, there is no known prevention.

Special concerns

Repeat surgery may be necessary for MFHs because these tumors sometimes redevelop. Careful monitoring by the medical team will be required.

Resources

ORGANIZATIONS

Center for Orthopedic Oncology and Musculoskeletal Research, Washington Cancer Institute. 110 Irving St. NW, Washington, DC 20010. (202) 877-3970. [cited July 5, 2005]. <http:// www.sarcoma.org>.

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Paul A. Johnson, Ed.M.

MALT lymphoma

Definition

MALT lymphomas are solid tumors that originate from cancerous growth of immune cells that are recruited to secretory tissue such as the gastrointestinal tract, salivary glands, lungs, and the thyroid gland.

Description

The digestive tract is generally not associated with lymphoid tissue, with the exception of small collections of lymphocytes such as Peyer's patches. A specific kind of white blood cell, B lymphocytes, can accumulate in response to infections of the digestive tract and other secretory tissues, or as a result of autoimmune conditions such as Sjögren's syndrome. When the growth of these lymphocytes is maintained through continued infection or autoimmune disease, a malignant cell can arise and replace the normal lymphocytes. These lymphomas, derived from mucosa-associated lymphoid tissue (MALT), most commonly arise in the stomach. Their growth seems to be dependent upon continuous stimulation of the immune system by an infectious agent, such as

H. pylori, or some other entity, termed an antigen, that the body recognizes as foreign. This antigen-driven growth permits these tumors to be treated by eliminating the stimulus that generated the original, normal **immune response**. In the stomach they are associated, in greater than 90% of all cases, with the bacteria called *Helicobacter pylori (H. pylori)*. This bacteria is also associated with peptic stomach irritation, ulcers, and gastric cancer. MALT lymphomas are generally indolent, that is, they grow slowly and cause little in the way of symptoms. Those MALT lymphomas that arise in the stomach in response to *H. pylori* infections are generally successfully treated with **antibiotics**, which eliminate the bacteria.

Demographics

MALT lymphomas occur at a frequency of about 1.5 per 100,000 people per year in the United States and account for about 10% of all **non-Hodgkin's lymphomas**. The frequency varies among different populations. For example, in parts of Italy the frequency of MALT lymphomas is as high as 13 per 100,000 people per year. This can in part be attributed to different rates of infection with *H. pylori*. However, other hereditary, dietary, or environmental factors are almost certainly involved.

Causes and symptoms

The majority of MALT lymphomas appear to be the result of infectious agents, most commonly *H. pylori* in the stomach. It is not known if infectious agents also cause MALT lymphomas outside of the stomach. In some cases, such as in the thyroid, MALT lymphomas seem to arise in patients who have autoimmune diseases, which make their immune systems treat their own tissue as foreign or antigenic. It is believed that there must be additional factors, in addition to infection or autoimmunity, that influence the development of MALT lymphomas. For example, in the United States, where infections with *H. pylori* are quite common, less than 1 in 30,000 people who have *H. pylori* in their stomachs develop MALT lymphomas. In addition, individuals who develop MALT lymphomas are more likely to develop other forms of cancer. This would suggest that there might be genetic factors predisposing individuals to develop MALT lymphomas or other tumors in response to environmental or infectious agents.

In general, patients have stomach pain, ulcers, or other localized symptoms, but rarely do they suffer from systemic complaints such as **fatigue** or **fever**.

Diagnosis

The indolent nature of most MALT lymphomas means that the majority of patients are diagnosed at early stages with relatively nonspecific symptoms. In the case of gastric MALT lymphomas, the physician will then have a gastroenterologist perform an endoscopy to examine the interior of the stomach. MALT lymphomas are then recognized as areas of inflammation or ulceration within the stomach. It is unusual for masses recognizable as tumors to be seen upon examination. Definitive diagnosis of MALT lymphoma requires a **biopsy**, in which a bit of tissue is removed from the stomach or other involved site. Examination of this tissue by a pathologist is the first step in distinguishing among the possible diagnoses of inflammation, indolent lymphoma, or a more aggressive form of cancer, such as gastric cancer or a rapidly growing non-Hodgkin's lymphoma. The pathologist evaluates the type of lymphoid cells that are present in the biopsy to establish the nature of the lesion. In addition, it is essential that the pathologist determine whether the lymphoma has grown beyond the borders of the mucosa, which lines the stomach or other gland.

KEY TERMS

Antigen—A foreign substance that leads to an immune response, including the production of antibodies by B cells.

Autoimmune disease—A condition in which an individual's immune system reacts to their own tissues, viewing self components as if they were foreign antigens.

Bone marrow biopsy—A procedure in which cellular material is removed from the pelvis or breastbone and examined under a microscope to look for the presence of abnormal blood cells characteristic of specific forms of leukemia and lymphoma.

Indolent lymphoma (also called low-grade)—Cancerous growths of lymphoid tissue that progress slowly to more aggressive forms of cancer.

Lymphoid tissue—Sites within the body that produce cells of the immune system, including lymph nodes, bone marrow, and the thymus.

Clinical staging, treatments, and prognosis

The best staging system to employ for MALT lymphomas is still the subject of discussion. However, it is standard practice that patients diagnosed with MALT lymphomas should be evaluated in a similar manner to individuals with nodal lymphomas, the more common type of lymphoma that originates at sites within the lymphoid system. These procedures include a complete

QUESTIONS TO ASK THE DOCTOR

- When will I know the results of the biopsies?
- Where does the lymphoma seem to be growing? Is there any evidence that it has spread?
- Does the pathology report indicate that this lymphoma is indolent? Will you treat me with antibiotics? Do you think chemotherapy or radiation is needed? Why?
- How long will I take the antibiotics or undergo chemotherapy before I am re-examined to see if the lymphoma is in remission?

history and physical, blood tests, chest x rays, and bone marrow biopsy. This evaluation will permit the oncologist to determine if the disease is localized or if it has spread to other sites within the body.

In general, the prognosis for patients with MALT lymphomas is good, with overall five-year survival rates that are greater than 80%. The features that are most closely related to the outlook for newly diagnosed individual patients are: whether the **primary site** is in the stomach or is extra-gastric; if the disease has spread beyond the initial location; and whether the histologic evaluation of the initial tumor biopsies is consistent with a low-grade, slowly growing lesion, as compared to a high-grade lesion that is more rapidly growing. In general, the histologic grade is the most important feature, with high-grade lesions requiring the most aggressive treatment.

Treatment of MALT lymphomas differs from that of most lymphomas. In the most common type of MALT lymphomas—low-grade lesions originating in the stomach—treatment with antibiotics to eliminate *H. pylori* leads to complete remissions in the majority of patients. The effectiveness of this treatment is indistinguishable from surgery, **chemotherapy**, **radiation therapy**, or a combination of surgery with drugs or irradiation. Approximately one-third of patients in this group have evidence of disseminated disease, where lymphoma cells are detected at sites in addition to the gastric mucosa. The response of these patients to antibiotic treatment is not significantly different from that for individuals with localized disease. For both groups a complete remission is achieved in about 75% of patients, who remain, on average, free of disease for about five years.

Patients with MALT lymphomas arising outside of the digestive tract also have good prognoses. Effective treatment for these lymphomas has been achieved with local radiation, chemotherapy, and/or interferons. Surgery followed by chemotherapy or radiation is also effective with nongastrointestinal MALT lymphomas. Overall these patients have five-year survival rates greater than 90%.

While the outlook for patients with MALT lymphomas is good, difficulties in diagnosis and staging have left the optimal treatment a matter of continued study. This is an especially open question for those patients who fail to respond to antibiotic therapy, or whose disease recurs. It may be the case that in these patients, the MALT lymphoma may have already progressed to a point where high-grade lesions, not observed in the original biopsies, were resistant to the initial treatment. The best treatment for these patients remains to be established. In general, these patients are treated with chemotherapy in a similar manner to patients with other types of lymphoma. Given the success of antibiotics, and the good prognosis for gastric MALT lymphomas in general, no sufficient body of evidence exists to determine the best chemotherapy for patients who fail to achieve a complete and lasting remission upon initial treatment. At present, a chemotherapeutic regime designated CHOP includes the anti-cancer drugs **cyclophosphamide**, **doxorubicin**, **vincristine**, and prednisone. Similar drug combinations are being used for patients whose MALT lymphomas do not respond to antibiotic treatment.

Clinical trials are underway and mostly concentrate upon optimizing treatment of gastric MALT lymphomas that involve *H. pylori*. The aspects of treatment being addressed are the most effective antibiotics and the use of antacids to modulate irritation in the stomach. These protocols have been designed to follow the natural history of gastric lymphomas and to establish the biological features that predict treatment response to antibiotics and duration of remission.

Prevention

There are currently no commonly accepted means to prevent MALT lymphomas. While the *H. pylori* infections are associated with this and other gastric disease, the eradication of *H. pylori* in asymptomatic individuals is not currently recommended for prevention of MALT lymphomas or stomach cancer.

Resources

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Warren Maltzman, Ph.D.

Mammography

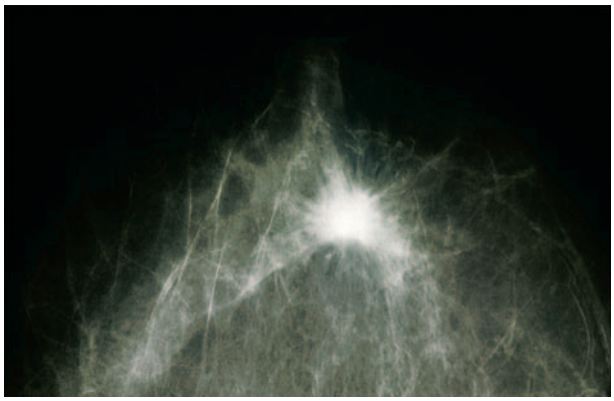
Definition

Mammography is the study of the breast using **x ray**. The actual test is called a mammogram. There are two types of mammograms. A screening mammogram is ordered for women who have no problems with their breasts. It consists of two x-ray views of each breast. A diagnostic mammogram is for evaluation of new abnormalities or of patients with a past abnormality requiring follow-up (i.e. a woman with **breast cancer** treated with **lumpectomy**). Additional x rays from other angles or special views of certain areas are taken.

Purpose

The purpose of screening mammography is breast cancer detection. A **screening test**, by definition, is used for patients without any signs or symptoms in order to detect disease as early as possible. Many studies have shown that having regular mammograms increases a woman's chances of finding breast cancer in an early stage, when it is more likely to be curable. It has been estimated that a mammogram may find a cancer as much as two years before it can be felt. The American Cancer Society, American College of Radiology, American College of Surgeons and American Medical Association recommend annual mammograms for every woman beginning at age 40.

Screening mammograms are not usually recommended for women under age 40 who have no special risk factors and a normal physical breast examination. Below age 40, breasts tend to be "radiographically dense," which means it is difficult to see many details. In 2003, a new technique that introduces radiographic contrast into digital mammograms was proving useful at improving visibility of breast cancer in younger women. Screening mammograms can detect cancers in their earliest stages and greatly reduce mortality, particularly among women age 40 to 69. In fact, a study in 2003 found that women age 40 and older who had annual screening mammograms had better breast cancer prognoses because their cancers were diagnosed at earlier stages than women who had mammograms less often.



A mammogram of the right breast of a 72-year-old woman reveals carcinoma. *(Custom Medical Stock Photo. Reproduced by permission.)*

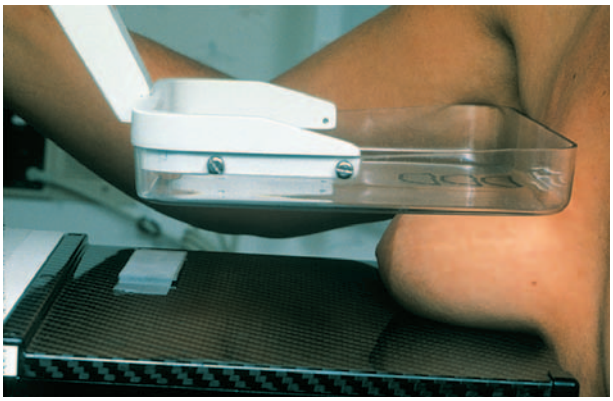
Some women are at increased risk for developing breast cancer, such as those with multiple relatives who have the disease. The 2003 American Cancer Society guidelines stated that women at increased risk might benefit from earlier screening mammograms and more frequent intervals for screening. However, the society suggested that evidence was not strong enough at that time to support making specific recommendations concerning screening examinations.

Diagnostic mammography is used to evaluate an existing problem, such as a lump, discharge from the nipple, or unusual tenderness in one area. The cause of the problem may be definitively diagnosed from this study, but further investigation using other methods often is necessary. This test is also used to evaluate findings from screening mammography tests.

Description

A mammogram may be offered in a variety of settings. Hospitals, outpatient clinics, physician's offices, or other facilities may have mammography equipment. In the United States, since October 1, 1994, only places certified by the U.S. Food and Drug Administration (FDA) are legally permitted to perform, interpret, or develop mammograms.

In addition to the usual paperwork, a woman will be asked to fill out a form seeking information relevant to her risk of breast cancer and special mammography needs. The woman is asked about personal and family history of cancer, details about menstruation, child bearing, birth control, breast implants, other breast surgery, age, and hormone replacement therapy. Information



Mammogram. Breast compressed with compression paddle. *(Copyright SIU, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

about Breast Self Examination (BSE) and other breast health issues are usually available at no charge.

At some centers, a technologist may perform a physical examination of the breasts before the mammogram. Whether or not this is done, it is essential for the patient to tell the technologist about any lumps, nipple discharge, breast pain, or other concerns.

Clothing from the waist up is removed and a hospital gown or similar covering is put on. The woman stands facing the mammography machine. The technologist exposes one breast and places it on a plastic or metal film holder about the size of a placemat. The breast is compressed as flat as possible between the film holder and a rectangle of plastic (called a paddle), which presses down onto the breast from above. The compression should only last a few seconds, just enough to take the x ray. Good compression can be uncomfortable, but it is necessary to ensure the clearest view of all breast tissues.

Next, the woman is positioned with her side toward the mammography unit. The film holder is tilted so the outside of the breast rests against it, and a corner touches the armpit. The paddle again holds the breast firmly as the x ray is taken. This procedure is repeated for the other breast. A total of four x rays, two of each breast, are taken for a screening mammogram. Additional x rays, using special paddles, different breast positions, or other techniques are usually taken for a diagnostic mammogram.

The mammogram may be seen and interpreted by a radiologist right away, or it may not be reviewed until later. If there are any questionable areas or an abnormality, extra x rays may be recommended. These may be taken during the same appointment. More commonly, especially for screening mammograms, the woman is called back on another day for these additional films.

KEY TERMS

Breast biopsy—A procedure in which suspicious tissue is removed and examined by a pathologist for cancer or other disease. The breast tissue may be obtained by open surgery or through a needle.

Radiographically dense—Difficult to see details of breast tissue on x ray.

A screening mammogram usually takes approximately 15 to 30 minutes. A woman having a diagnostic mammogram can expect to spend up to an hour at the mammography facility.

The cost of mammography varies widely. Many mammography facilities accept "self referral." This means women can schedule themselves without a physician's referral. However, some insurance policies do require a doctor's prescription to ensure payment. Medicare will pay for annual screening mammograms for all women with Medicare who are age 40 or older and a baseline mammogram for those age 35 to 39.

A digital mammogram is performed in the same way as a traditional exam, but in addition to the image being recorded on film, it is viewed on a computer monitor and stored as a digital file.

Preparation

The compression or squeezing of the breast for a mammogram is a concern for some women, but necessary to render a quality image. Even with concerns about pain, a 2003 study said that three-fourths of women reported the pain associated with a mammogram as four on a 10-point scale. Mammograms should be scheduled when a woman's breasts are least likely to be tender. One week after the menstrual period is usually best. The MQSA regulates equipment compression for consistency and performance.

Women should not put deodorant, powder, or lotion on their upper body on the day the mammogram is performed. Particles from these products can get on the breast or film holder and may look like abnormalities on the mammogram film.

Aftercare

No special aftercare is required.

Risks

The risk of radiation exposure from a mammogram is considered virtually nonexistent. Experts are unani-

QUESTIONS TO ASK THE DOCTOR

- What do the results mean?
- If there is something abnormal, shouldn't we immediately find out what it is?
- What future care will I need?

mous that any negligible risk is far outweighed by the potential benefits of mammography.

Some breast cancers do not show up on mammograms, or "hide" in dense breast tissue. A normal (or negative) study is not a guarantee that a woman is cancer-free. Mammograms find about 85% to 90% of breast cancers.

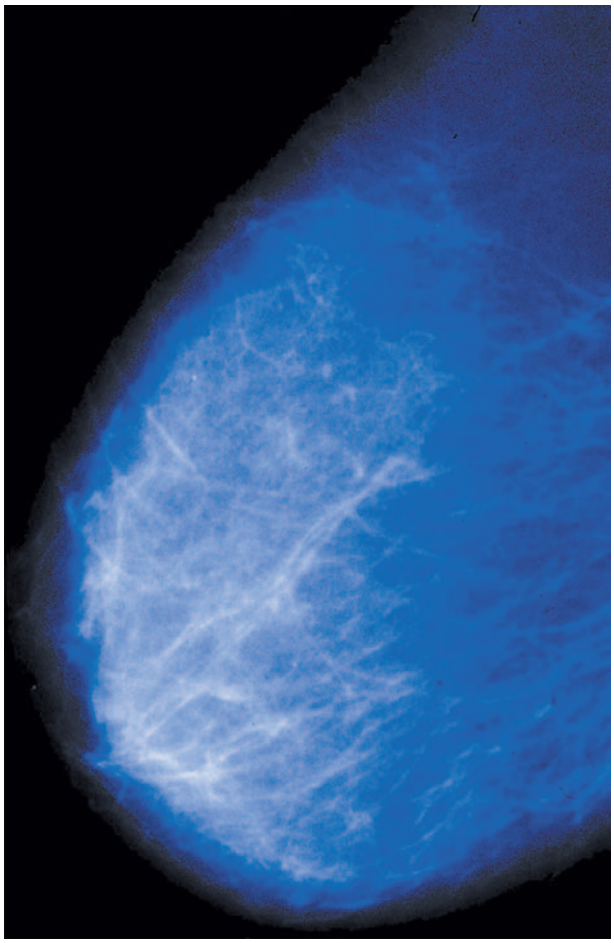
"False positive" readings are also possible, and 5% to 10% of mammogram results indicate the need for additional testing, most of which confirms that no cancer is present.

Normal results

A mammography report describes details about the x ray appearance of the breasts. It also rates the mammogram according to standardized categories, as part of the Breast Imaging Reporting and Data System (BIRADS) created by the American College of Radiology (ACR). A normal mammogram may be rated as BIRADS 1 or negative, which means no abnormalities were seen. A normal mammogram may also be rated as BIRADS 2 or benign findings. This means that one or more abnormalities were found but are clearly benign (not cancerous), or variations of normal. Some kinds of calcification, lymph nodes, or implants in the breast might generate a BIRADS 2 rating. A BIRADS 0 rating indicates that the mammogram is incomplete and requires further assessment.

Abnormal results

Many mammograms are considered borderline or indeterminate in their findings. BIRADS 3 means an abnormality is present and probably (but not definitely) benign. A follow-up mammogram within a short interval of six months is suggested. This helps to ensure that the abnormality is not changing, or is "stable." This stability in the abnormality indicates that a cancer is probably not present. If the abnormality were a cancer, it would have grown in the interval between mammograms. Some women are uncomfortable or anxious about waiting and may want to consult with their doctor about a having a biopsy. BIRADS 4 means suspicious for cancer. A biopsy is usually recommended in this case. BIRADS 5 means an abnormality is highly suggestive of cancer. The suspicious area should be biopsied.



Color-enhanced mammogram of the left breast of a 73-year-old woman showing normal tissue. *(Copyright SIU, Science Source/Photo Researchers, Inc. Photo reproduced by permission.)*

Often, screening mammograms are followed up with additional imaging. The reasons are numerous; they may mot mean the radiologist suspects a cancerous lesion, only that he or she cannot make a clear diagnosis from the screening mammogram views. The most common imaging methods are additional views on the mammogram, sometimes called magnification views, and ultrasound. In recent years, some patients have received magnetic resonance imaging (MRI) of the breast. A new technique called dual-energy contrast enhanced digital subtraction mammography is reported to find cancers that may be missed by conventional mammography. It may be ordered in the future as a follow-up study.

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"Contrast Mammography Reveals Hard-to-find Cancers." *Cancer Weekly* (October 14, 2003): 34.

Henderson, Craig. *Mammography & Beyond. Developing Technologies for the Early Detection of Breast Cancer: A Non-technical Summary*. Washington, DC: National Academy Press, 2001.

Love, Susan M., with Karen Lindsey. *Dr. Susan Love's Breast Book*. 3rd ed. Boulder, CO: Perseus Book Group, 2000.

PERIODICALS

Smith, Robert A., et al. "American Cancer Society Guidelines for Breast Cancer Screening: Update 2003." *Cancer* May-June 2003: 141-170.

ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd., Atlanta, GA 30329. (800) ACS-2345. <http://www.cancer.org>.

Federal Drug Administration. 5600 Fishers lane, Rockville, MD 20857. (800) 532-4440. <http://www.fda.gov>.

National Cancer Institute. Office of Cancer Communications. Bldg. 31, Room 10A31, Bethesda, MD 20892. NCI/ Cancer Information Service: (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

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Teresa G. Odle

Mantle cell lymphoma

Definition

Mantle cell lymphoma (MCL) is a rare type of non-Hodgkin's lymphoma characterized under the microscope by expansion of the mantle zone area of the lymph node with a homogeneous (structurally similar) population of malignant small lymphoid cells. These cancerous cells have slightly irregular nuclei and very little cytoplasm, and are mixed with newly made normal lymphocytes (white blood cells) that travel from the bone marrow to the lymph nodes and spleen. Unlike normal lymphocytes, they do not mature properly and become cancerous instead.

Description

The body's immune system produces two types of lymphocytes or white blood cells: the B cells which are made in the bone marrow and the T cells which are made in the thymus. Both types of cells are found in the lymph, the clear liquid that bathes tissues and circulates in the lymphatic system. Lymphomas are cancers that occur in this lymphatic system and B-Cell lymphomas—also called non-Hodgkin's lymphomas—include follicular lymphomas, small non-cleaved cell lymphomas (Burkitt's lymphomas), marginal zone lymphomas (MALT lymphomas), small lymphocytic lymphomas, large cell lymphomas and also mantle cell lymphomas.

Mantle cell lymphoma accounts for 5% to 10% of all lymphomas diagnosed and 5% of B-cell lymphomas. There are three subsets of MCL cells: the mantle zone type, the nodular type, and the blastic or blastoid (immature) type. These various types often occur together to some degree, and approximately 30% to 40% of diagnoses are of mixed mantle and nodular type. As MCL develops further, the non-cancerous mantle centers also become invaded by cancerous cells. In about 20% of these cases, the cells become larger, and of the blastic type.

Extensive debates are ongoing concerning the grade of this cancer. European classification used to classify it as a low-grade cancer because it is initially slow-growing, while American classification considered it intermediate based on patients' shorter average survival rate. The combined European-American classification (REAL), is still discussing the status of mantle cell lymphoma. This is due to the mixed nature of MCL cells. Blastic type-MCL seems to be considered as a high-grade cancer because it spreads at about the rate of other lymphomas belonging to that category. The studies currently attempting to describe the precise nature of these cells will be key to any general agreement that is finally reached.

Demographics

Mantle cell lymphoma is rare in persons under the age of 50. It is most often seen in men aged 50–70 years. Out of 1,000 persons diagnosed with MCL, approximately 33% will be women. This cancer has the shortest average survival of all lymphoma types.

Causes and symptoms

The cause of MCL is unknown. Many of its symptoms are shared by other lymphomas as well and patients generally complain of **fatigue**, **anemia**, low grade fevers, **night sweats**, **weight loss**, rashes, digestive disturbances, chronic sinus irritation, recurrent infections, sore throat, shortness of breath, muscle and bone aches and edema.

More specific symptoms include spleen enlargement (in about 60% to 80% of cases), particularly with nodu-

lar-type MCL. Swollen lymph nodes are an early-stage symptom, even though the general health of the patient is good. Mild anemia is also common. Some patients also report lower back pain, and burning pain in the legs and testicles. As MCL becomes more advanced, the lymph nodes increase in volume, and the general symptoms become more pronounced.

In the end stage of MCL, neurologic symptoms appear, indicating that the MCL has spread to the central nervous system.

Diagnosis

MCL is very similar to several other lymphoma types and special care must be taken with the diagnosis. It should not be made from blood or bone marrow specimens alone. It is believed that immunologic tests are required to make the correct diagnosis. Immunophenotyping is one such test, it is used to determine what kind of surface molecules are present on cells, and thus, the exact type of lymphoma from a tissue sample. The Lymphoma Research Foundation of America recommends that several opinions be sought from recognized mantle cell experts to confirm the accuracy of the diagnosis.

At the time of diagnosis, mantle cell lymphoma has usually spread into other tissues such as the lymph nodes, spleen, bone marrow (up to 90% of cases), or to Waldeyer's ring (the ring of adenoid, palatine and lingual tonsils at the back of the mouth) or to the gastrointestinal tract. MCL can also spread to the colon, in which case it is diagnosed as multiple lymphomatous polyposis.

Treatment team

Depending on the type of MCL and stage of the cancer, the treatment team may include a radiation oncologist, a medical oncologist, a surgeon and a neurologist.

Clinical staging, treatments, and prognosis

There is no formal staging system for mantle cell lymphoma and no standard treatment has yet been adopted for MCL patients. Patients have been treated with surgery, radiation, single drug or combination **chemotherapy** and stem cell transplants. CHOP is one of the most common chemotherapy regimens for treating MCL. It derives its name from the combination of drugs used: **Cyclophosphamide** (cytoxan, neosar), adriamycin (**doxorubicin** or Hydroxydoxorubicin), **vincristine** (Oncovin), and Prednisone.

There is no cure for mantle cell lymphoma. As with other slow-growing lymphomas, spontaneous remissions have been reported, but only partial, lasting a year at the most. All mantle cell lymphoma experts agree that the long-term prognosis of MCL patients receiving conventional treatment is poor, and that there is an urgent need for new, improved therapies.

Alternative and complementary therapies

Because MCL is a cancer of the lymphatic system, immunologic therapies are often used, or combined with the more conventional radiation and chemotherapy treatments. Immunological therapies take advantage of the body's immune system. The immune system is a network of specialized cells and organs that defends the body against foreign invaders (antigens) by producing special ''defense'' proteins, an example of which are the antibodies. These substances recognize and attach to the antigens, usually found on the surface of cells and destroy them. There are reports of immunological therapies being used for MCL using interferon, one such natural substance produced by the body in response to a virus. Numerous studies show that **interferons** can stimulate the immune system to fight the growth of cancer, but there has not yet been enough evidence produced to see it emerge as a strong candidate for MCL treatment.

Other immunological therapies based on **monoclonal antibodies** (MABs or MOABs) have recently emerged, such as Rituxan (**rituximab**). MABs work on cancer cells in the same way natural antibodies work, by identifying and binding to the target cells, alerting other cells in the immune system to the presence of the cancer cells. MABs are very specific for a particular antigen, meaning that one designed for a B-cell lymphoma will not work on T-cell lymphomas. MABs used alone may enhance a patient's **immune response** to the cancer but they are thought to be more efficient when combined to another form of therapy, such as a chemotherapeutic drug. This way, the cancer is attacked on two fronts: chemical attack from the chemotherapy and immune response attack stimulated by the MAB.

Coping with cancer treatment

It is important to have a caregiver system when receiving medical treatment for MCL, and it is just as important to have a network of support for coping with the non-medical aspects of the cancer. Friends, relatives, coworkers and health professionals all can provide help, as well as the national cancer associations, some specifically addressing the needs of lymphoma patients. Please refer to the Resources section at the end of this entry for contact information.

KEY TERMS

Anemia—A condition caused by a reduction in the amount of red blood cells produced by the bone marrow. Its symptoms are general weakness and lack of energy, dizziness, shortness of breath, headaches, and irritability.

Antibody—A protein (immunoglobulin) produced by plasma cells (mature B cells) to fight infections in the body. They are released into the circulatory system in response to specific antigens and thus target those antigens that induced their production.

Antigen—An antigen is any substance which elicits an antibody response. As such, they are substances that stimulate a specific immune response of the body and are capable of reacting with the products of that response. Antigens may be foreign chemical substances or proteins located on the surface of viruses, bacteria, toxins, tumors and other infectious agents.

B-Cell lymphocyte—A type of lymphocyte (white blood cell). B cells react to the presence of antigens by dividing and maturing into plasma cells.

B-cell lymphomas—Non-Hodgkin's lymphomas that arise from B cells.

Blood cell—Cellular component of blood. There are three general types: white blood cells, red blood cells, and platelets, all which are produced in the bone marrow.

Cytoplasm—The organized complex of organic and inorganic substances external to the nuclear membrane of a cell.

DNA—Deoxyribonucleic acid are nucleic acids that are the part of the cell nucleus that contains and controls all genetic information.

Edema—Swelling of a body part caused by an abnormal buildup of fluids.

Gene—The specific site on a chromosome, consisting of protein and DNA responsible for the transmittal and determination of hereditary characteristics.

Gene therapy—The use of genes to treat cancer and other diseases.

Immune system—The system within the body, consisting of many organs and cells, that recognizes and fights foreign cells and disease.

Lymph—A milky white liquid responsible for carrying the lymphocytes in the lymphatic vessels.

Lymphatic system—Tissues and organs such as the bone marrow, spleen, thymus and lymph nodes that produce and store cells to fight infection and disease. Also includes the lymphatic vessels that carry lymph.

Lymphocyte—A type of white blood cell that defends the body against infection and disease. Lymphocytes are found in the bloodstream, the lymphatic system, and lymphoid organs. The two main types of lymphocytes are the B cells (produced in the bone marrow) and the T cells (produced in the thymus).

Lymphoma—Cancers that starts in the lymphatic system. Lymphomas are classified into two categories: Hodgkin's Disease and the non-Hodgkin's lymphomas.

Monoclonal antibody—An antibody raised against a specific antigen. Monoclonal antibodies are being used to target chemotherapy or radioactive substances directly to cancer cells.

Non-Hodgkin's lymphomas—Lymphomas characterized by different types of cancerous lymphatic cells, excluding those characterized by Hodgkin's disease.

Remission—A complete or partial disappearance of the signs and symptoms of cancer, usually in response to treatment.

Stem cell—Primitive cell found in the bone marrow and in the blood stream. Stem cells become different types of mature blood cells, thus enabling them to rejuvenate the circulatory and immune systems.

Stem cell transplant—Treatment procedure by which young blood stem cells are collected from the patient (autologous) or another matched donor (allogeneic). High-dose chemotherapy and/or radiation is given, and the stem cells are reinserted into the patient to rebuild his or her immune system.

Clinical trials

Clinical trials addressing the needs of MCL patients are very recent because the mantle cell lymphoma subtype has only recently been defined. There are now several trials being carried out in the United States specifically for mantle cell. Some other trials designed for patients with lymphomas may also accept mantle cell patients. Ongoing trials in this area are cheifly concerned with investigating monoclonal antibodies. Information regarding clinical trials can be obtained through the Clinical Trials web site listed at the end of this entry.

The following clinical protocols are specifically designed for MCL patients:

- The MD Anderson Protocol (high-dose chemotherapy with or without stem cell transplant)
- Rituxan, by itself or with CHOP
- Bexxar
- Oncolym
- Flavopiridol
- Phenylacetate

Prevention

Because the cause of MCL is unknown, no prevention measures can be recommended.

Special concerns

Special concerns that apply to lymphoma patients may also apply to MCL patients. Because MCL is a cancer that usually involves chemotherapy and **radiation therapy**, it can be severely damaging to organ function and long-term resistance. In addition to the immediate side effects of these treatments, other effects appear after treatment is completed, one of which, called Post-Cancer Fatigue (PCF), is often seen with lymphoma patients. This is fatigue that persists after treatment and can sometimes be extreme. The medical team will be able to offer the best advice to deal with PCF.

See also Acute lymphocytic leukemia; Central nervous system lymphomas.

Resources

PERIODICALS

Grosfeld, J. L. "Risk-based Management of Solid Tumors in Children." *American Journal of Surgery* 180 (November 2000): 322–7.

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The Leukemia and Lymphoma Society. 1311 Mamaroneck Ave. White Plains, N.Y., 10605. (914) 949-5213. [cited July 5, 2005]. <http://l3.leukemia-lymphoma.org/hm_lls>.

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Monique Laberge, Ph.D.

Mastectomy

Definition

Mastectomy is the surgical removal of the breast for the treatment or prevention of **breast cancer**.

Purpose

Mastectomy is performed as a surgical treatment for breast cancer. The severity of a breast cancer is evaluated according to a complex system called staging. This takes into account the size of the tumor and whether it has spread to the lymph nodes, adjacent tissues, and/or distant parts of the body. A mastectomy usually is the recommended surgery for more advanced breast cancers. Women with earlier stage breast cancers, who might also have breast-conserving surgery (**lumpectomy**), may choose to have a mastectomy. In the United States, approximately 50,000 women a year undergo mastectomy.

The size, location, and type of tumor are important considerations when choosing the best surgery to treat breast cancer. The size of the breast is also an important factor. A woman's psychological concerns and lifestyle choices should also be considered when making a decision.

There are many factors that make a mastectomy the treatment of choice for a patient. Large tumors are difficult to remove with good cosmetic results. This is especially true if the woman has small breasts. Sometimes multiple areas of cancer are found in one breast, making removal of the whole breast necessary. The surgeon is sometimes unable to remove the tumor with a sufficient amount, or margin, of normal tissue surrounding it. In this situation, the entire breast needs to be removed. Recurrence of breast cancer after a lumpectomy is another indication for mastectomy.

Radiation therapy is almost always recommended following a lumpectomy. If a woman is unable to have radiation, a mastectomy is the treatment of choice. Pregnant women cannot have radiation therapy for fear of harming the fetus. A woman with certain collagen vascular diseases, such as systemic lupus erythe-

matosus or scleroderma, would experience unacceptable scarring and damage to her connective tissue from radiation exposure. Any woman who has had therapeutic radiation to the chest area for other reasons cannot tolerate additional exposure for breast cancer therapy.

The need for radiation therapy after breast-conserving surgery may make mastectomy more appealing for nonmedical reasons. Some women fear radiation and choose the more extensive surgery so radiation treatment will not be required. The commitment of time, usually five days a week for six weeks, may not be acceptable for other women. This may be due to financial, personal, or job-related factors. In geographically isolated areas, a course of radiation therapy may require lengthy travel and perhaps unacceptable amounts of time away from family or other responsibilities.

Some women choose mastectomy because they strongly fear recurrence of the breast cancer, and lumpectomy seems too risky. Keeping a breast that has contained cancer may feel uncomfortable for some patients. They prefer mastectomy, so the entire breast will be removed.

The issue of prophylactic or preventive mastectomy, or removal of the breast to prevent future breast cancer, is controversial. Women with a strong family history of breast cancer and/or who test positive for a known cancer-causing gene may choose to have both breasts removed. Patients who have had certain types of breast cancers that are more likely to recur may elect to have the unaffected breast removed. Although there is some evidence that this procedure can decrease the chances of developing breast cancer, it is not a guarantee. It is not possible to be certain that all breast tissue has been removed. There have been cases where breast cancers have occurred after both breasts have been removed.

Studies have shown that women who choose preventive mastectomy generally are satisfied with their choice, but also believe they lacked enough information before deciding, particularly about the surgery, genetic testing, and breast reconstruction. A study released in 2003 concerning women who underwent radical mastectomy of one breast and chose surgical removal of the other breast as a preventive measure found that 83% were highly satisfied with their decision.

Precautions

The decision to have mastectomy or lumpectomy should be carefully considered. It is important that the woman be fully informed of all the potential risks and benefits of each surgical treatment before making a choice.

Description

There are several types of mastectomies. The radical mastectomy, also called the Halsted mastectomy, is rarely performed today. It was developed in the late 1800s, when it was thought that more extensive surgery was most likely to cure cancer. A radical mastectomy involves removal of the breast, all surrounding lymph nodes up to the collarbone, and the underlying chest muscle. Women were often left disfigured and disabled, with a large defect in the chest wall requiring skin grafting, and significantly decreased arm sensation and motion. Unfortunately, and inaccurately, it is still the operation many women picture when the word mastectomy is mentioned.

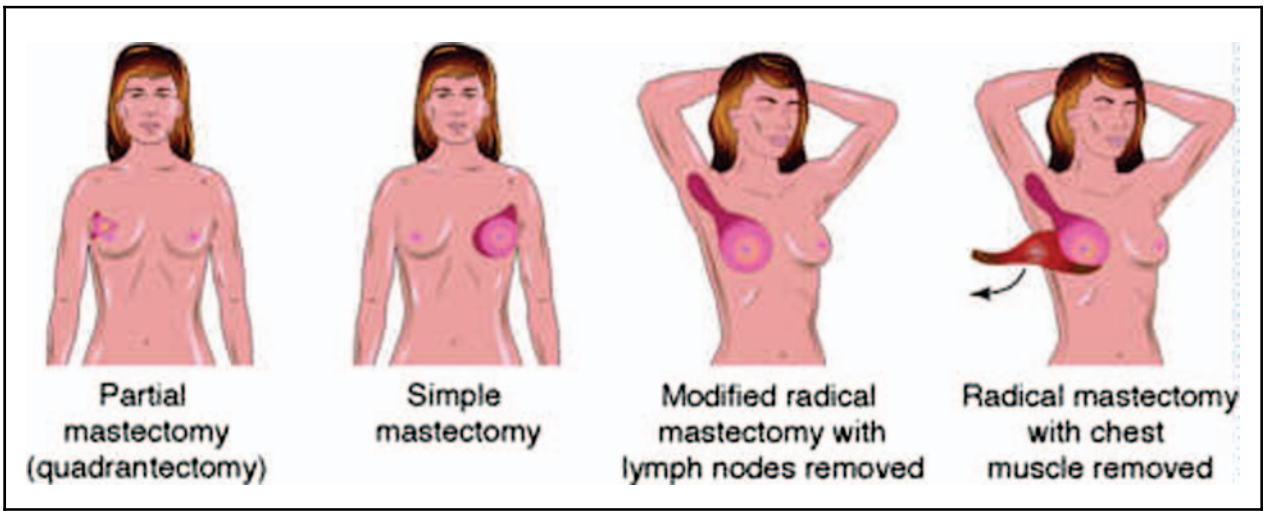
Surgery that removes breast tissue, nipple, an ellipse of skin, and some axillary or underarm lymph nodes, but leaves the chest muscle intact, is usually called a modified radical mastectomy. This is the most common type of mastectomy performed today. The surgery leaves a woman with a more normal chest shape than the older radical mastectomy procedure, and a scar that is not visible in most clothing. It also allows for immediate or delayed breast reconstruction.

In a simple mastectomy, only the breast tissue, nipple, and a small piece of overlying skin are removed. If a few of the axillary lymph nodes closest to the breast are also taken out, the surgery may be called an extended simple mastectomy.

There are other variations on the term mastectomy. A skin-sparing mastectomy uses special techniques that preserve the patient's breast skin for use in reconstruction, although the nipple is still removed. Total mastectomy is a confusing expression, as it may be used to refer to a modified radical mastectomy or a simple mastectomy. In 2003, surgeons reported on a new technique that spared the nipple in many women with early stage breast cancer.

Many women choose to have breast reconstruction performed in conjunction with the mastectomy. The reconstruction can be done using a woman's own abdominal tissue, or using saline-filled artificial expanders, which leave the breast relatively flat but partially reconstructed. Additionally, there are psychological benefits to coming out of the surgery with the first step to a reconstructed breast. Immediate reconstruction will add time and cost to the mastectomy procedure, but the patient can avoid the physical impact of a later surgery.

A mastectomy is typically performed in a hospital setting, but specialized outpatient facilities sometimes are used. The surgery is done under general anesthesia. The type and location of the incision may vary according to plans for reconstruction or other factors, such as old



There are four types of mastectomies: partial mastectomy, or lumpectomy, in which the tumor and surrounding tissue is removed; simple mastectomy, where the entire breast and some axillary lymph nodes are removed; modified radical mastectomy, in which the entire breast and axillary lymph nodes are removed; and the radical mastectomy, where the entire breast, axillary lymph nodes, and chest muscles are removed. *(Illustration by Electronic Illustrators Group.)*

scars. As much breast tissue as possible is removed. Approximately 10 to 20 axillary lymph nodes are usually removed. All tissue is sent to the pathology laboratory for analysis. If no immediate reconstruction is planned, surgical drains are left in place to prevent fluid accumulation. The skin is sutured and bandages are applied.

The surgery may take from two to five hours. Patients usually stay at least one night in the hospital, although outpatient mastectomy is increasingly performed for about 10% of all patients. Insurance usually covers the cost of mastectomy. If immediate reconstruction is performed, the length of stay, recovery period, insurance reimbursement, and fees will vary. In 1998, the Women's Health and Cancer Rights Act required insurance plans to cover the cost of breast reconstruction in conjunction with a mastectomy procedure.

Preparation

Routine preoperative preparations, such as not eating or drinking the night before surgery, typically are ordered for a mastectomy. On rare occasions, the patient also may be asked to donate blood in case a blood transfusion is required during surgery. The patient should advise the surgeon of any medications she is taking. Information regarding expected outcomes and potential complications also should be part of preparation for a mastectomy, as for any surgical procedure. It is especially important that women know about sensations they might experience after surgery, so they are not misinterpreted as a sign of poor wound healing or recurrent cancer.

Aftercare

In the past, women often stayed in the hospital at least several days. Now many patients go home the same day or within a day or two after their mastectomies. Visits from home care nurses can sometimes be arranged, but patients need to learn how to care for themselves before discharge from the hospital. Patients may need to learn to change bandages and/or care for the incision. The surgical drains must be attended to properly; this includes emptying the drain, measuring fluid output, moving clots through the drain, and identifying problems that need attention from the doctor or nurse. If the drain becomes blocked, fluid or blood may collect at the surgical site. Left untreated, this accumulation may cause infection and/or delayed wound healing.

After a mastectomy, activities such as driving may be restricted according to individual needs. Pain is usually well controlled with prescribed medication. Severe pain may be a sign of complications, and should be reported to the physician. A return visit to the surgeon is usually scheduled seven to 10 days after the procedure.

Exercises to maintain shoulder and arm mobility may be prescribed as early as 24 hours after surgery. These are very important in restoring strength and promoting good circulation. However, intense exercise should be avoided for a time after surgery in order to prevent injury. The specific exercises suggested by the physician will change as healing progresses. Physical therapy is an integral part of care after a mastectomy, aiding in the overall recovery process.

KEY TERMS

Axillary—Located in or near the armpit.

Lymphedema—Swelling caused by an accumulation of fluid from faulty lymph drainage.

Mastectomy, modified radical— Total mastectomy with axillary lymph node dissection, but with preservation of the pectoral muscles.

Mastectomy, radical—Removal of the breast, pectoral muscles, axillary lymph nodes, and associated skin and subcutaneous tissue.

Mastectomy, simple—Removal of only the breast tissue, nipple and a small portion of the overlying skin.

QUESTIONS TO ASK THE DOCTOR

- What are my options for degree of treatment? Is it advisable to consider lumpectomy instead of a mastectomy procedure?
- What are the cosmetic implications of this surgery? What are my options for reconstruction?
- How soon after the procedure will I be able to return to normal activities?
- Is there a support group in the area where I could talk with other women who have undergone this procedure?

Emotional care is another important aspect of recovery from a mastectomy. A mastectomy patient may feel a range of emotions including **depression**, negative self-image, grief, fear and anxiety about possible recurrence of the cancer, anger, or guilt. Patients are advised to seek counseling and/or support groups and to express their emotions to others, whether family, friends, or therapists. Assistance in dealing with the psychological effects of the breast cancer diagnosis, as well as the surgery, can be invaluable for women.

Measures to prevent injury or infection to the affected arm should be taken, especially if axillary lymph nodes were removed. There are a number of specific instructions directed toward avoiding pressure or constriction of the arm. Extra care must be exercised to avoid injury, to treat it properly if it occurs, and to seek medical attention promptly when appropriate.

Additional treatment for breast cancer may be necessary after a mastectomy. Depending on the type of tumor, lymph node status, and other factors, **chemotherapy**, radiation therapy, and/or hormone therapy may be prescribed.

Risks

Risks that are common to any surgical procedure include bleeding, infection, anesthesia reaction, or unexpected scarring. After mastectomy and axillary **lymph node dissection**, a number of complications are possible. A woman may experience decreased feeling in the back of her armpit or other sensations including numbness, tingling, or increased skin sensitivity. Some women report phantom breast symptoms, experiencing **itching**, aching, or other sensations in the breast that has been removed. There may be scarring around where the lymph nodes were removed, resulting in decreased arm mobility and requiring more intense physical therapy.

Approximately 10% to 20% of patients develop lymphedema after axillary lymph node removal. This swelling of the arm, caused by faulty lymph drainage, can range from mild to very severe. It can be treated with elevation, elastic bandages, and specialized physical therapy. Lymphedema is a chronic condition that requires continuing treatment. This complication can arise at any time, even years after surgery. A new technique called **sentinel lymph node mapping** and **biopsy** can eliminate the need for removing many lymph nodes.

Normal results

A mastectomy is performed as the definitive surgical treatment for breast cancer. The goal of the procedure is that the breast cancer is completely removed and does not recur.

Abnormal results

An abnormal result of a mastectomy is the incomplete removal of the breast cancer or a recurrence of the cancer. Other abnormal results include long-lasting (chronic) pain or impairment that does not improve after several months of physical therapy.

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National Lymphedema Network. 2211 Post St., Suite 404, San Francisco, CA 94115-3427. (800) 541-3259 or (415) 921-1306. <http://www.wenet.net/~lymphnet/>.

Y-ME National Organization for Breast Cancer Information and Support. 18220 Harwood Ave., Homewood, IL 60430. 24-hour hotlines: (800) 221-2141 or (708) 799-8228.

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Matrix metalloproteinase inhibitors

Definition

Matrix metalloproteinases are a class of enzymes that can break down proteins, such as collagen and gelatin. Since these enzymes require zinc or calcium atoms to function, they are referred to as metalloproteinases. Matrix metalloproteinases function in tumor cell invasion and **metastasis**, wound healing, and angiogenesis (supplying the tumor with blood). They are normally found in the spaces between cells (extracellular) in tissues and are involved in degrading extracellular matrix proteins like collagens and gelatins. The extracellular matrix compartments are the primary barriers to tumor growth and spread. Matrix metalloproteinase inhibitors are selective inhibitors of matrix metalloproteinases. These agents inhibit tumor metastasis and angiogenesis.

Description

Matrix metalloproteinases have been linked to cancers such as breast, ovarian, colorectal, and lung. Synthetic matrix metalloproteinase inhibitors are being explored for use in **cancer prevention** and treatment because of their demonstrated antimetastatic and antiangiogenic properties. Matrix metalloproteinase inhibitors include compounds such as: Marimastat (BB-2516), COL-3, BAY 12-9566, and KB-R7785. Marimastat (BB-2516) was the first orally bioavailable matrix metalloproteinase inhibitor to enter **clinical trials** in the field of oncology. Developing nontoxic, orally active, MMP inhibitors is important because these compounds will likely need chronic administration in combination with other therapies.

Crystal Heather Kaczkowski, MSc.

Mechlorethamine

Definition

Mechlorethamine is a **chemotherapy** medicine used to treat cancer by destroying cancerous cells. Mechlorethamine is marketed as the brand name Mustargen. It is also commonly known as nitrogen mustard.

Purpose

Mechlorethamine is approved by the Food and Drug Administration (FDA) to treat **Hodgkin's disease** and **non-Hodgkins' lymphomas**. It is also approved for certain types of leukemia, malignant lymphomas, and lung cancer. Mechlorethamine has been used to relieve symptoms caused by a build up of cancerous fluid in the lungs, abdomen, and around the heart.

Description

Mechlorethamine is one of the first chemotherapy drugs discovered to have an effect on cancer cells. **Clinical trials** with this agent began in the 1940s. Mechlorethamine is a member of the group of chemotherapy drugs known as alkylating agents. Alkylating agents interfere with the genetic material (DNA) inside the cancer cells, more specifically through cross-linking DNA strands, and prevent them from further dividing and growing more cancer cells. Mechlorethamine is commonly combined with other chemotherapy agents to treat cancer.

Recommended dosage

A mechlorethamine dose can be determined using a mathematical calculation that measures a person's body surface area (BSA). This number is dependent upon a patient's height and weight. The larger the person, the

greater the body surface area. BSA is measured in the units known as square meter (m^2). The body surface area is calculated and then multiplied by the drug dosage in milligrams per square meter (mg/m^2). This calculates the actual dose a patient is to receive.

Mechlorethamine is a yellowish liquid that is injected directly into a vein over a period of one to five minutes. It can also be applied onto the skin as an ointment for certain conditions.

Mechlorethamine is combined with other chemotherapeutic drugs **vincristine** (oncovin), **procarbazine**, and prednisone for treatment of Hodgkin's disease. The dose of mechlorethamine used in this regimen is 6 mg per square meter on day 1 and day 8 of a treatment cycle. This regimen is referred to as MOPP, and was one the initial regimens that caused a breakthrough in the treatment of Hodgkin's disease.

Mechlorethamine can also be infused into certain compartments in the body where cancerous fluid has accumulated. The dose for this treatment is based on a patient's weight in kilograms (1 kilogram is 2.2 pounds). Mechlorethamine is given at a dose of 0.2 to 0.4 mg per kilogram of body weight, infused directly into the area where the fluid is building up.

KEY TERMS

Anemia—A red blood cell count that is lower than normal.

Antidote—A drug given to reverse the negative effects of another drug.

Chemotherapy—Specific drugs used to treat cancer.

Deoxynucleic acid (DNA)—Genetic material inside of cells that carries the information to make proteins that are necessary to run the cells and keep the body functioning smoothly.

Food and Drug Administration (FDA)—The government agency that oversees public safety in relation to drugs and medical devices, and gives the approval to pharmaceutical companies for commercial marketing of their products.

Intravenous—To enter the body through a vein.

Metastatic—Cancer that has spread to one or more parts of the body.

Neutropenia—A white blood cell count that is lower than normal.

Precautions

Patients should notify their doctors if they have had any previous allergic reactions to chemotherapy treatment or if they have received **radiation therapy**.

Blood counts should be monitored regularly while on mechlorethamine therapy. During a certain time period after receiving mechlorethamine, there may be an increased risk of getting infections. Caution should be taken to avoid unnecessary exposure to crowds and people with infections.

Patients who may be pregnant or are trying to become pregnant should tell their doctors before receiving mechlorethamine. Chemotherapy can cause men and women to become sterile, or unable to have children.

Patients should check with their doctors before receiving live virus **vaccines** while on chemotherapy.

Patients should increase their intake of fluids while on this medication.

Side effects

One of the most common side effects from receiving mechlorethamine is **nausea and vomiting**. The nausea and vomiting can begin within one hour from receiving the drug. Patients will be given **antiemetics** before and after receiving mechlorethamine to help prevent or decrease this side effect.

A common side effect from taking mechlorethamine is low blood cell counts (**myelosuppression**). When the white blood cell count is lower than normal (**neutropenia**), patients are at an increased risk of developing **fever** and infections. The platelet blood count can also be decreased. Platelets are blood cells in the body that cause clots to form to stop bleeding. When the platelet count is low, patients are at an increased risk for bruising and bleeding. Low red blood cell counts (**anemia**), make people feel tired, dizzy, and lacking in energy.

Less common side effects from mechlorethamine include **diarrhea**, loss of appetite (anorexia), mouth sores, liver problems, metallic taste in the mouth, fever, ringing in the ears or hearing loss, and inflammation at the injection site. Allergic reactions have been reported, some of them severe anaphylactic reactions.

Damage to nerves and nervous system tissues is uncommon with mechlorethamine therapy. However, some reports do exist of nerve damage that has resulted in numbness and tingling in the hands and feet.

Mechlorethamine can cause skin reactions. When applied on top of the skin, the area can become red, swollen, brown colored, itchy, and have a burning sensation.

Hair loss (**alopecia**), irritation, and change of color of the vein where the drug was injected can occur. If the drug is not given directly into the vein, or is accidentally injected into surrounding areas of tissue, an antidote must be administered to that area as soon as possible. The area will become painful, gray-colored, and the tissue will begin to die. This is considered a severe reaction, and medical personnel must be notified immediately.

Interactions

Radiation therapy along with mechlorethamine administration can cause severe damage to the bone marrow.

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Meclizine

Definition

Meclizine is an antihistamine commonly used to control nausea, vomiting and dizziness. It is known by the over-the-counter name Bonine. In the United States, the prescription brand name is Antivert.

Purpose

Meclizine may be given to help control **nausea and vomiting** that often occurs with cancer treatment, other medical conditions, or motion sickness. It is also used as part of palliative care for patients with terminal cancer.

More recently, meclizine has been reported to be effective in the treatment of panic disorder.

Description

Meclizine acts as a central nervous system depressant. It is believed its therapeutic actions occur due to the drug's drying effects and its ability to depress conduction of nerve messages in the inner ear. Meclizine begins working about one hour after ingestion. It continues being effective for eight to 24 hours.

Recommended dosage

The dosage to control nausea and vomiting associated with cancer treatment is 25 mg to 50 mg, every eight to 12 hours. When used to manage dizziness, patients generally take 25 mg to 100 mg daily in divided doses. Patients should not double up on this medication if a dose is missed.

Precautions

Patients with glaucoma, an enlarged prostate, bladder or bowel obstructions, or asthma or other breathing difficulties should discuss with the doctor the risks and benefits associated with this drug before taking it. Those who have experienced an allergic reaction to meclizine should not take it. The FDA recommends that youngsters under age 12 should not take this drug, except under the direction of a physician. Pregnant women and those trying to become pregnant should not take this medication. Animal reproductive studies have shown some deformities at elevated doses. Women who are breastfeeding should discuss this medication with their doctors prior to taking it.

Side effects

Meclizine may cause drowsiness and **fatigue**. Drowsiness is the most common adverse reaction. Alcohol and other central nervous system depressants, such as pain medication and tranquilizers, may increase this effect. Patients should refrain from drinking alcoholic beverages, and avoid driving or operating machinery or appliances when taking this drug. Less frequently, the drug also may produce the opposite effect. Excitability, nervousness, restlessness, mood enhancement and difficulty sleeping may develop. Rarely, it may cause a patient to see or hear things that are not present (hallucinations). Despite being used to treat nausea and vomiting, it may produce this effect. It may also cause constipation, **diarrhea**, an upset stomach or a poor appetite (anorexia). Other side effects include frequent or difficult urination, incomplete emptying of the bladder, low blood pressure, a rapid heart rate or palpitations. It may cause vision changes, a dry nose and throat, ringing in the ears, and a rash or hives. Some of the side effects may be more pronounced in older adults.

Side effects may decrease as the body adjusts to the medication. Ice chips or sugarless hard candy or gum may help relieve the dry mouth. If the feeling of a dry mouth persists for more than two weeks, the doctor should be notified.

Interactions

Central nervous system depressants, including alcohol, may increase drowsiness associated with meclizine. Pain medications, other antihistamines, seizure

KEY TERMS

Antihistamine—Agent that blocks or counteracts the action of histamine, which is released during an allergic reaction.

Palliative—Referring to treatments that are intended to relieve pain and other symptoms of disease but not to cure.

medications, sleeping pills and muscle relaxants can depress the central nervous system. Taking this drug with some medications used to treat **depression** may increase the risk of side effects. Patients should inform the doctor of all medications being taken. Patients should not start or stop any drugs without the approval of the doctor. The herbal supplement henbane may increase some of meclizine's side effects, including dry mouth and difficulty urinating.

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Mediastinal tumors

Definition

A mediastinal tumor is a growth in the central chest cavity (mediastinum), which separates the lungs and contains the heart, aorta, esophagus, thymus, and trachea. Mediastinal tumors are also known as neoplasms of the mediastinum.

Description

Growths that originate in the mediastinum are called primary mediastinal tumors. Most of them are composed of reproductive (germ) cells or develop in thymic, neurogenic (nerve), lymphatic, or mesenchymal (soft) tissue.

Secondary (metastatic) mediastinal tumors originate in the lung, stomach, esophagus, and trachea, and spread through the lymphatic system to the chest cavity.

Although still relatively rare, malignant mediastinal tumors are becoming more common. Usually diagnosed in patients between 30 and 50 years old, they can develop at any age and arise from any tissue that exists in or passes through the chest cavity.

The mediastinum is traditionally divided into superior, anterior, middle, and posterior compartments, and is also described as having anterosuperior, middle, and posterior divisions. Boundaries of these divisions are not fixed, and they frequently overlap.

The anterosuperior compartment contains a vein and the thymus gland, superior vena cava, aortic arch, and thyroid gland. More than half (54%) of mediastinal tumors in adults and 43% of those in children occur in the anterosuperior compartment.

The middle mediastinum contains the pericardium, heart, nerves of the diaphragm (phrenic nerves), trachea, main bronchial stem, and lung hila. Twenty percent of adult mediastinal tumors and 18% of those in children occur in this division.

The posterior mediastinum contains the sympathetic chain, vagus nerve (which controls the heart, larynx, and gastrointestinal tract), thoracic duct (which drains lymph from the abdomen, legs, and left side of the head and chest), descending thoracic aorta, and the esophagus. Slightly more than one fourth (26%) of adult mediastinal tumors and 40% of those in children occur in the posterior mediastinum.

Each of these compartments also contains lymph nodes and fatty tissue.

Types of cancers

Anterior mediastinal tumors

The most common anterior mediastinal tumors are thymomas, teratomas, lymphomas, and thyroid tissue that has become enlarged or displaced (ectopic).

THYMOMAS The cause of most adult mediastinal tumors and 15% of those in children, thymomas almost always form at the spot where the heart and great vessels meet. These tumors usually develop between the ages of 40 and 60.

About half of the people who have thymomas do not have any symptoms. Between 35 and 50% experience symptoms of **myasthenia gravis**, such as

- weakness of the eye muscles
- drooping of one or both eyelids (ptosis)
- fatigue

Early treatment of these slow-growing tumors is very effective. Most are benign, but thymomas can metastasize and should always be considered cancerous.

TERATOMAS Most common in young adults, teratomas are made up of embryonic (germ) cells that did not develop normally and do not belong in the part of the body where the tumor is located. Found along the center of the body between the skull and kidneys, teratomas account for:

- 10%–15% of primary mediastinal tumors
- 70% of **germ cell tumors** in children
- 60% of germ cell tumors in adults

Teratomas may be solid or contain cysts. Malignant teratomas usually develop between the ages of 30 and 40, and almost all (90%) of them occur in men.

At least 90% of patients with these tumors experience:

- chest pain
- cough
- fever
- shortness of breath

These symptoms may not appear until the tumor has grown very large.

LYMPHOMAS These tumors account for 10–20% of anterior mediastinal tumors. Although lymphomas are the second most common mediastinal tumor in children, they are usually diagnosed between the ages of 30 and 40. Nonsclerosing **Hodgkin's disease** causes most adult mediastinal lymphomas.

Some patients with lymphomas do not have symptoms. Others cough or experience chest pain.

THYROID TUMORS Most mediastinal thyroid tumors grow out of goiters and occur in women between the ages of 50 and 60. About 75% of these tumors extend to the windpipe (trachea). The rest extend behind it.

Mediastinal thyroid tumors are encapsulated and do not metastasize.

Middle mediastinal tumors

Tumors of the middle mediastinum include lymphomas, mesenchymal tumors, and carcinomas.

MESENCHYMAL TUMORS Also called soft tissue tumors, mesenchymal tumors originate in connective tissue within the chest cavity. These tumors account for about 6% of primary mediastinal tumors. More than half (55%) of them are malignant.

The most common mesenchymal tumors are lipomas, liposarcomas, fibromas, and fibrosarcomas.

Posterior mediastinal tumors

Tumors of the posterior mediastinum include: neurogenic tumors, mesenchymal tumors, and endocrine tumors.

NEUROGENIC TUMORS Representing 19–39% of mediastinal tumors, neurogenic tumors can develop at any age. They are most common in young adults.

Adult neurogenic tumors are usually benign. In children, they tend to be malignant and tend to metastasize before symptoms appear.

MALIGNANT SCHWANNOMAS Also known as malignant sheath tumors, malignant sarcomas, and neurosarcomas, these tumors develop from the tube (sheath) enclosing the peripheral nerves that transmit impulses from the central nervous system (CNS) to muscles and organs.

Usually large and painful, these rare, aggressive tumors may invade the lungs, bones, and aorta.

NEUROBLASTOMAS The most common malignant tumors of early childhood, neuroblastomas generally occur before the age of two. These tumors usually develop in the adrenal glands, neck, abdomen, or pelvis.

Neuroblastomas often spread to other organs. Most patients have symptoms that relate to the part of the body the tumor has invaded. Likelihood of survival is greatest in patients who are less than a year old and whose tumor has not spread.

Symptoms

About 40% of people who have mediastinal tumors do not have any symptoms. When symptoms exist, they usually result from pressure on an organ that the tumor has invaded, and indicate that the tumor is malignant.

The symptoms most commonly associated with mediastinal tumors are:

- chest pain
- cough
- shortness of breath

A person who has a mediastinal tumor may be hoarse, cough up blood (**hemoptysis**), or have:

- fatigue
- difficulty swallowing (dysphagia)
- night sweats
- systemic lupus erythematosus
- inflamed muscles (polymyositis)
- ulcerative colitis
- rheumatoid arthritis
- thyroid problems (thyroiditis, thyrotoxicosis,)
- fever
- glandular disorders (panhypopituitarism, adenopathy)
- high blood pressure
- low blood sugar (hypoglycemia)
- breast development in males (gynecomastia)
- wheezing
- vocal cord paralysis
- heart problems (**superior vena cava syndrome**, pericardial tamponade, arrhythmias)
- neurologic abnormalities
- weight lossand other immune, autoimmune, and endocrine system disorders.

Blood disorders associated with these tumors include abnormally high levels of calcium (**hypercalcemia**), abnormally low numbers of:

- circulating blood cells (cytopenia)
- normal red blood cells (pernicious anemia)
- antibodies (hypogammaglobulinemia)and an inability to produce red blood cells (red-cell aplasia).

Diagnosis

Imaging studies

Routine x rays often detect mediastinal tumors. Doctors use **computed tomography** (CT) scans of the chest to determine tumor size and location, extent of disease, the tumor's relationship to nearby organs and tissues, and whether the tumor contains cysts or areas of calcification.

Magnetic resonance imaging (MRI) is more effective at clarifying the relationship between a tumor and nearby blood vessels, but is far more costly and time-consuming than CT scanning.

Other tests

Injecting radioactive substances into the patient's blood (radioimmunoassay) enables doctors to measure levels of hormones and other substances a tumor secretes and identify specific tumor types, evaluate the effectiveness of therapy, and monitor possible tumor recurrence.

Invasive procedures

Imaging studies play the most important role in initial diagnosis of mediastinal tumors, but before doctors can determine the most effective treatment for any tumor, they must know what kind of cells it contains.

Although invasive diagnostic procedures have been largely replaced by less invasive techniques (such as CT-guided percutaneous needle **biopsy**), some patients still require surgery.

MEDIASTINOSCOPY Performed under general anesthesia, this relatively simple procedure enables doctors to accurately diagnose 80–90% of mediastinal tumors, and 95–100% of anterior mediastinal tumors.

Mediastinoscopy is especially useful in providing the large tissue specimens needed to diagnose lymphomas.

MEDIASTINOTOMY Doctors perform mediastinotomy by using a lighted tube to:

- examine the center of the chest and nearby lymph nodes
- remove tissue for biopsy
- determine whether cancer has spread from the spot where it originated. Similar to mediastinoscopy, this procedure begins with a small incision next to the breastbone, rather than in the patient's neck.

Mediastinotomy also enables doctors to examine the lymph nodes closest to the heart and lungs. Cancer that originates in the left upper lobe of the lung often spreads to these nodes.

THORACOTOMY Although some surgeons still perform this procedure to diagnose mediastinal tumors, thoracoscopy may be used instead in certain situations. In a **thoracotomy**, the physician gains access to the chest cavity by cutting through the chest wall. Thoracotomy allows for study, examination, treatment, or removal of any organs in the chest cavity. Tumors and metastatic growths can be removed, and a biopsy can be taken, through the incision. Thoracotomy also gives access to the heart, esophagus, diaphragm, and the portion of the aorta that passes through the chest cavity.

THORACOSCOPY This 100% accurate, minimally invasive procedure is performed under general anesthesia. Enabling the surgeon to view the entire mediastinum, **thoracoscopy** may be used when a mediastinal tumor touches the mediastinal pleura. However, this procedure has limited applications.

Thoracoscopy cannot be performed on a patient who has thick scar tissue.

Treatment

Doctors use surgery, radiation, and single-agent or combination **chemotherapy** to treat mediastinal tumors.

Thymomas

A patient whose **thymoma** is surgically removed (resected) has the best chance of survival. To lessen the likelihood of new tumors developing (reseeding), surgeons do not recommend biopsy, and try to remove the tumor without puncturing the capsule that encloses it.

RADIATION Thymomas respond well to radiation, which is used:

- to treat all stages of disease
- before or after surgical resection
- to treat recurrent disease.

The course of treatment lasts three to six weeks. The most common complications of **radiation therapy** are formation of scar tissue in the lungs (pulmonary fibrosis), inflammation of the pericardium (pericarditis), and inflammation of the spinal cord (myelitis).

CHEMOTHERAPY The use of chemotherapy to treat invasive thymomas is becoming more common. One or more drugs may be administered before or after surgery. Synthetic hormones (**corticosteroids**) can reverse the progression of tumors that do not respond to chemotherapy.

Teratomas

Teratomas are removed surgically. Chemotherapy and radiation are not used to treat these tumors. The prospect for long-term cure is excellent, and these tumors rarely recur.

Lymphomas

These tumors do not require surgery, except to make the diagnosis. Doctors treat them with chemotherapy and radiation.

Thyroid tumors

Doctors generally treat thyroid tumors with surgical resection, chemotherapy, and/or radiation.

Mediastinal tumors

Cancer type	Occurs in
Thymomas	Anterior mediastinum, almost always form where heart and major vessels meet
Teratomas	Anterior mediastinum, along the center of the body between the skull and kidneys
Lymphomas	Anterior and middle mediastinum
Thyroid tumors	Thyroid (anterior mediastinum)
Mesenchymal tumors (soft tissue tumors)	Middle mediastinum
Carcinomas	Middle mediastinum
Neurogenic tumors (developing in nerve cells)	Posterior mediastinum
Malignant schwannomas	Posterior mediastinum
Neuroblastomas	Posterior mediastinum

Fibrosarcomas

Fibrosarcomas cannot usually be resected and do not respond well to chemotherapy.

Malignant schwannomas

Multiagent chemotherapy is used to treat these aggressive tumors, which tend to recur following surgery. The 5-year survival rate is 75%.

Neuroblastomas

Because these tumors sometimes regress spontaneously, doctors may postpone treatment if the patient has no symptoms or the tumor is not growing.

In other cases, doctors remove these tumors even before symptoms appear. Risks associated with removing these tumors from the spinal canal include:

- injury to the spinal cord or anterior spinal artery
- uncontrolled bleeding in the spinal canal
- decreased blood supply (ischemia) to tissues and organs.

See also CT-guided biopsy; Fibrosarcoma; Neuroblastoma; Thyroid cancer.

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Maureen Haggerty

Mediastinoscopy

Definition

Mediastinoscopy is a surgical procedure that allows physicians to view areas of the mediastinum, the cavity behind the breastbone that lies between the lungs. The organs in the mediastinum include the heart and its vessels, the lymph nodes, trachea, esophagus, and thymus.

Mediastinoscopy is most commonly used to detect or stage cancer. It is also ordered to detect infection, and to confirm diagnosis of certain conditions and diseases of the respiratory organs. The procedure involves insertion of an endotracheal (within the trachea) tube, followed by a small incision in the chest. A mediastinoscope is inserted through the incision. The purpose of this equipment is to allow the physician to directly see the organs inside the mediastinum, and to collect tissue samples for laboratory study.

Purpose

Mediastinoscopy is often the diagnostic method of choice for detecting **lymphoma**, including **Hodgkin's disease**. The diagnosis of sarcoidosis (a chronic lung disease) and the staging of lung cancer can also be accomplished through mediastinoscopy. Lung cancer staging involves the placement of the cancer's progression into stages, or levels. These stages help a physician study cancer and provide consistent definition levels of cancer and corresponding treatments. The lymph nodes in the mediastinum are likely to show if lung cancer has spread beyond the lungs. Mediastinoscopy allows a physician to observe and extract a sample from the nodes for further study. Involvement of these lymph nodes indicates diagnosis and stages of lung cancer.

Mediastinoscopy may also be ordered to verify a diagnosis that was not clearly confirmed by other methods, such as certain radiographic and laboratory studies. Mediastinoscopy may also aid in certain surgical biopsies of nodes or cancerous tissue in the mediastinum. In fact, the surgeon may immediately perform a surgical procedure if a malignant tumor is confirmed while the patient is undergoing mediastinoscopy, thus combining the diagnostic exam and surgical procedure into one operation when possible.

Although still performed in 2001, advancements in **computed tomography** (CT) and **magnetic resonance imaging** (MRI) techniques, as well as the new developments in **ultrasonography**, have led to a decline in the use of mediastinoscopy. In addition, better results of fine-needle aspiration (drawing out fluid by suction) and core-needle **biopsy** (using a needle to obtain a small tissue sample) investigations, along with new techniques in **thoracoscopy** (examination of the thoracic cavity with a lighted instrument called a thoracoscope) offer additional options in examining mediastinal masses. Mediastinoscopy may be required, however, when these other methods cannot be used or when the results they provide are inconclusive.

Precautions

Because mediastinoscopy is a surgical procedure, it should only be performed when the benefits of the exam's findings outweigh the risks of surgery and anesthesia. Patients who previously had mediastinoscopy should not receive it again if there is scarring present from the first exam.

Several other medical conditions, such as impaired cerebral circulation, obstruction or distortion of the upper airway, or thoracic aortic aneurysm (abnormal dilation of the thoracic aorta) may also preclude mediastinoscopy. Anatomic structures that can be compressed by the mediastinoscope may complicate these pre-existing medical conditions.

Description

Mediastinoscopy is usually performed in a hospital under general anesthesia. An endotracheal tube is inserted first, after local anesthesia is applied to the throat. Once the patient is under general anesthesia, a small incision is made usually just below the neck or at the notch at the top of the breastbone. The surgeon may clear a path and feel the patient's lymph nodes first to evaluate any abnormalities within the nodes. Next, the physician will insert the mediastinoscope through the incision. The scope is a narrow, hollow tube with an attached light that allows the surgeon to see inside the area. The surgeon can insert tools through the hollow tube to help perform biopsies. A sample of tissue from the lymph nodes or a mass can be extracted and sent for study under a microscope or on to a laboratory for further testing.

In some cases, analysis of the tissue sample which shows malignancy will suggest the need for immediate surgery while the patient is already prepared and under anesthesia. In other cases, the surgeon will complete the visual study and tissue extraction and stitch the small incision closed. The patient will remain in the surgery recovery area until it is determined that the effects of anesthesia have lessened and it is safe for the patient to leave the area. The entire procedure should take about an hour, not counting preparation and recovery time. Studies have shown that mediastinoscopy is a safe, thorough,

KEY TERMS

Endotracheal—Placed within the trachea, also known as the windpipe.

Hodgkin's disease—A malignancy of lymphoid tissue found in the lymph nodes, spleen, liver, and bone marrow.

Lymph nodes—Small round structures located throughout the body; contain cells that fight infections.

Pleural space—Space between the layers of the pleura (membrane lining the lungs and thorax).

Sarcoidosis—A chronic disease characterized by nodules in the lungs, skin, lymph nodes and bones; however, any tissue or organ in the body may be affected.

Thymus—An unpaired organ in the mediastinal cavity that is important in the body's immune response.

QUESTIONS TO ASK THE DOCTOR

- Why do I need this test?
- Is the test dangerous?
- How do I prepare for the test?
- How long will the test take?
- Will I get general or local anesthesia?
- How soon will I get my test results?

and cost-effective diagnostic tool with less risk than some other procedures.

Preparation

Patients are asked to sign a consent form after having reviewed the risks of mediastinoscopy and known risks or reactions to anesthesia. The physician will normally instruct the patient to fast from midnight before the test until after the procedure is completed. A physician may also prescribe a sedative the night before the exam and before the procedure. Often a local anesthetic will be applied to the throat to prevent discomfort during placement of the endotracheal tube.

Aftercare

Following mediastinoscopy, patients will be carefully monitored to watch for changes in vital signs or indications of complications of the procedure or the anesthesia. A patient may have a sore throat from the endotracheal tube, temporary chest pain, and soreness or tenderness at the site of incision.

Risks

Complications from the actual mediastinoscopy procedure are relatively rare—the overall complication rate in various studies has been 1.3–3.0%. However, the following complications, in decreasing order of frequency, have been reported:

- hemorrhage
- pneumothorax (air in the pleural space)
- recurrent laryngeal nerve injury, causing hoarseness
- infection
- tumor implantation in the wound
- phrenic nerve injury (injury to a thoracic nerve)
- esophageal injury
- chylothorax (chyle—a milky lymphatic fluid—in the pleural space)
- air embolism (air bubble)
- transient hemiparesis (paralysis on one side of the body)

The usual risks associated with general anesthesia also apply to this procedure.

Normal results

In the majority of procedures performed to diagnose cancer, a normal result involves evidence of small, smooth, normal-appearing lymph nodes and no abnormal tissue, growths, or signs of infection. In the case of lung cancer staging, results are related to the severity and progression of the cancer.

Abnormal results

Abnormal findings may indicate lung cancer, tuberculosis, the spread of disease from one body part to another, sarcoidosis (a disease that causes nodules, usually affecting the lungs), lymphoma (abnormalities in the lymph tissues), and Hodgkin's disease.

Resources

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PERIODICALS

Deslauriers, Jean, and Jocelyn Gregoire. "Clinical and Surgical Staging of Non-Small Cell Lung Cancer." *Chest,* Supplement (April 2000): 96S–103S.

Tahara R. W., et al. "Is There a Role for Routine Mediastinoscopy in Patients With Peripheral T1 Lung Cancers?" *American Journal of Surgery* (December 2000): 488–491.

ORGANIZATIONS

Alliance for Lung Cancer Advocacy, Support, and Education. P.O. Box 849, Vancouver, WA 98666. 800–298–2436. <http://www.alcase.org>.

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. 800–ACS–2345 <http://www.cancer.org>.

American Lung Association. 1740 Broadway, New York, NY 10019–4374. 800–LUNG–USA (800–586–4872). <http://www.lungusa.org>.

Teresa G. Odle

Medroxyprogesterone acetate

Definition

Medroxyprogesterone acetate (MPA) is used during cancer therapy to stop new cell growth in some cancers. It is also used outside of cancer treatment as a contraceptive. MPA is known by many different brand names in the United States including Amen, Depo-Provera, Provera, Prodasone, and Progeston.

Purpose

MPA is used to treat some advanced, hormone-responsive cancers of the breast, kidney, and lining of the uterus.

Description

MPA is a synthetic derivative of the female hormone progesterone. In healthy women, progesterone plays a major role in preparing the uterus for pregnancy. MPA has been approved by the Food and Drug Administration (FDA), and its use in cancer treatment is usually covered by insurance. Outside the area of cancer treatment, it is used to prevent pregnancy.

Exactly why MPA stops tumor growth is unclear. Many cancerous tumors are sensitive to hormones. It appears that MPA, in some way, changes the hormonal climate of the tumor so that cells stop responding to other hormones and proteins that would normally stimulate their growth. This drug cannot tell the difference between normal cells and cancer cells, so some normal cells are also killed during treatment. But since cancer cells generally grow more rapidly than normal cells, more cancer cells are killed. MPA is considered very effective and relatively non-toxic.

MPA is usually given to women whose **breast cancer** has returned or whose cancer does not respond to **tamoxifen** or **toremifene**. Both drugs are antiestrogens, or agents that antagonize the actions of estrogen. For these women, it is an alternative to the new aromatase inhibiting drugs (anastrozole, letrozole, or aromasin). Aromatase is one of the enzymes involved in steroid biosynthesis. In **endometrial cancer** (cancer of the uterus), MPA is sometimes used when cancer has spread (metastasized) beyond the uterus or is inoperable.

Recommended dosage

MPA comes as tablets or as a liquid that is given as an intramuscular injection. For breast cancer, it is usually given as a tablet once a day at the same time each day. Occasionally, MPA is given in divided doses that are spaced evenly throughout the day. For kidney and uterine cancer, MPA is usually given as a shot once a week at first, then later once a month.

By 2001, **clinical trials** were underway testing the use of MPA in women with both breast and endometrial cancer. The selection of clinical trials underway changes frequently. Current information on clinical trials and where they are being held is available by entering the search term "medroxyprogesterone acetate" at the following web sites:

- National Cancer Institute <http://cancertrials.nci.nih.gov> or (800) 4-CANCER
- National Institutes of Health Clinical Trials <http://clinicaltrials.gov>
- Center Watch: A Clinical Trials Listing <http://www.centerwatch.com>

Precautions

People taking MPA daily should take it at the same time each day. The time of day is unimportant, but the regular spacing of the dose is important.

Women taking MPA should not get pregnant. It is believed that MPA causes birth defects in babies born to mothers who are taking this drug during the first four months of pregnancy.

Side effects

The number and severity of side effects vary widely among people. Not only is it dependent on each person's

KEY TERMS

Endometrial cancer—Cancer of the uterus.

Food and Drug Administration (FDA)—The government agency that oversees public safety in relation to drugs and medical devices, and gives the approval to pharmaceutical companies for commercial marketing of their products.

own unique body chemistry, side effects vary with the type of cancer, the health of the patient, and the other drugs being given. There is no way to predict who will experience side effects of MPA.

Among the more common side effects are:

- increased appetite and weight gain
- nausea
- swelling and fluid retention in the hands, legs, and breast
- breakthrough vaginal bleeding
- muscle cramps
- fatigue
- emotional or mood changes
- headaches

A less common, but serious, side effect is the development of blood clots that can lead to heart attack or stroke. People who have a history of clotting problems are not good candidates for using MPA.

Interactions

Aminoglutethimide (Cytadren: an inhibitor of steroid biosynthesis), when given with MPA, decreases the effectiveness of MPA.

Tish Davidson, A.M.

Medulloblastoma

Definition

Medulloblastoma is a solid, cancerous tumor originating in the cerebellum of the brain. It is also known as a primitive neuroendocrine tumor.

Description

Medulloblastoma is the most common cancerous brain tumor of childhood. It accounts for 20% to 25% of all childhood tumors. Medulloblastomas can occur soon after birth and into puberty, but most tumors occur either before age ten or sometime in the late teens or early twenties. If these tumors are left untreated, they can spread to other areas of the brain and to the spine.

Medulloblastomas occur in the area of the brain known as the cerebellum. The cerebellum, located in the back of the brain above the neck, is the area of the brain responsible for controlling and integrating movement. A person could move his or her muscles without the aid of the cerebellum, but those movements would be clumsy and disorganized. Medulloblastoma tumors in the cerebellum can cause loss of functioning of the cerebellum, leading to this uncoordinated movement, called cerebellar ataxia.

If medulloblastomas are not detected early, they may spread cancer throughout the brain or spinal cord. If the cancer spreads to the spinal cord, a child may begin experiencing severe back pain, difficulty walking, and the inability to control bladder and bowel functions.

Demographics

As stated earlier, medulloblastoma is a childhood cancer, occurring mainly in the first ten years of life. About half of all medulloblastomas occur in children aged five or younger. Boys tend to develop the tumors more than girls at a rate of approximately two to one. There are no current studies comparing the incidence of medulloblastoma between different racial and ethnic groups.

Causes and symptoms

Besides being male, there are no other known risk factors for medulloblastoma. This type of tumor can occur in association with two rare types of genetically linked family cancer syndromes. Gorlin's syndrome and Turcot's syndrome. Gorlin's syndrome is caused by a defect in a gene known as PTC located on chromosome 9. This defect can cause medulloblastoma as well as cancers of the skin and ovary. Turcot's syndrome is caused by a defective gene known as APC, and can present with cancer of the intestinal tract as well as medulloblastoma. It should again be stated that both of these syndromes are quite rare and only account for a fraction of medulloblastoma cases seen and reported.

Medulloblastoma can present in many ways. In infants, symptoms of the tumor can include an unusual increase in head size, vomiting, irritability, and lethargy. Since all infants generally have these symptoms at one

time or another, it can be difficult for a parent or even a health care worker to recognize the initial presentation of medulloblastoma in babies and toddlers.

In older children and teenagers, medulloblastoma can present the same as in infants or much differently. Non-specific symptoms such as **nausea and vomiting**, headache, and vague visual disturbances can be the first sign of a tumor in the cerebellum. Other, more striking signs can be double vision, sudden difficulty writing, and problems walking and moving that worsen over time.

Diagnosis

The diagnosis of medulloblastoma is made with both clinical observation and **imaging studies**. If a parent has noticed some of the signs and symptoms listed above, then a visit to a pediatrician is certainly warranted. During the office visit, various specialized neurological tests will be done to see if there is any sign of a problem in the cerebellum or surrounding brain structures.

If there are indications of a tumor, then imaging studies can be done to see if a tumor can be detected. The two types of imaging studies done to detect medulloblastoma are **magnetic resonance imaging** (MRI) and computed tomography (CT) scan. The MRI uses a high-strength magnetic field to visualize the brain, and is very useful for detecting medulloblastomas. The CT scan uses **x-ray** images reconstructed by computer. Like the MRI, a CT scan is also useful for detecting brain tumors as well as tumors that may have spread to the spine.

Treatment team

The treatment of medulloblastoma is optimally carried out in a medical center that has experience in treating this often difficult-to-treat cancer. Treatment and treatment planning is usually carried out by a multidisciplinary team of cancer specialists, including a pediatric oncologist (a doctor specializing in the treatment of **childhood cancers**), a pediatric neurosurgeon (a doctor specializing in childhood brain surgery), as well as a pediatric neurologist and radiation oncologist (a doctor specializing in the use of radiation to treat cancer).

Clinical staging, treatment, and prognosis

The staging of childhood brain tumors has become important to the selection of treatment plans, as well as giving information to make a more accurate prognosis. For medulloblastoma, there are four stages defined, as follows:

- T1: the tumor is less than 3 cm in diameter.
- T2: the tumor is greater than 3 cm in diameter and has invaded one other brain structure in addition to the cerebellum.
- T3: the tumor has invaded two other brain structures besides the cerebellum.
- T4: the tumor has spread down into the midbrain or upper spinal cord.

The treatment options for medulloblastoma have changed significantly over the past few decades. The first treatment option for medulloblastoma was surgery, and this is still the most common treatment. Surgeons try to remove the entire tumor, although this is sometimes not possible. After the surgery is completed, further treatment will depend upon whether or not the child has been placed in an "average risk" or "high risk" group. An average-risk child is defined as three years or older, with the tumor initially confined to the cerebellum with little to no tumor left after surgery. A high-risk child is defined as a child under three years of age, with the tumor initially spread into other areas of the brain besides the cerebellum, and with some of the tumor remaining in the brain after surgery.

Children in the average-risk group will often have radiation therapy applied to the area in their brain where the medulloblastoma tumor was, especially if the surgeon was not able to remove all of the tumor. Using radiation on children younger than three years may result in the child having growth retardation along with learning disabilities.

Because of the possible side effect of radiation, especially in children younger than three years of age, the use of certain medications called **chemotherapy** is being used more frequently for medulloblastoma. Researchers have found that medulloblastoma tumors are highly sensitive to chemotherapy, giving hope that chemotherapy can be used instead of radiation, especially for children at average risk. For children at high risk, the current recommendation is to use both radiation and chemotherapy, since this combination has been shown to improve overall survival rates for high-risk children.

In 1930, the anticipated survival rate for a child with medulloblastoma after surgery was less than 2%. Today, with the use of better surgical techniques, radiation, and chemotherapy, the prognosis for children in the average risk group has increased to a 60% survival rate over a five-year period. Children in the high-risk group do not fare as well, having a 30% to 35% survival rate over a five-year period.

KEY TERMS

Ataxia—The inability to perform voluntary, coordinated muscular movements.

Cerebellum—The portion of the brain lying superior to the spinal cord, involved in coordinating voluntary muscular movements.

Chemotherapy—The application of certain medicinal chemicals to treat specific diseases, including cancer.

Radiation therapy—The use of high-energy ionizing radiation in the treatment of cancerous tumors.

Alternative and complementary therapies

Alternative and complementary therapies are those that fall outside the scope of traditional, first-line therapies such as surgery, chemotherapy and radiation. Complementary therapies are meant to supplement those traditional therapies with the objective of relieving symptoms. Alternative therapies are nontraditional, unproven attempts to cure the disease.

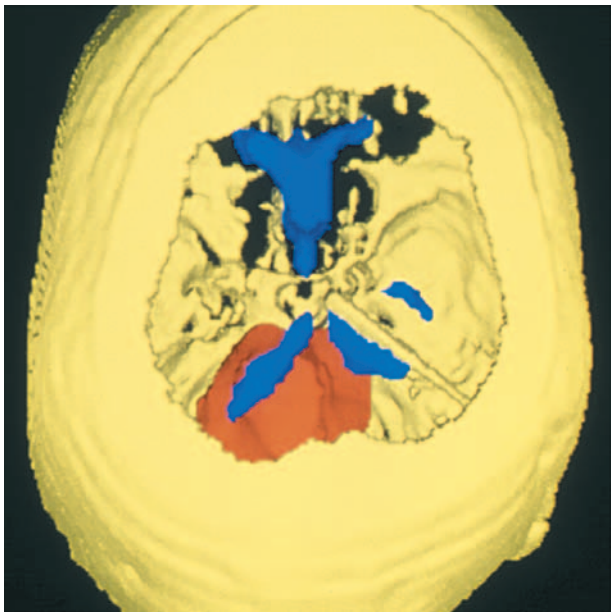
Common complementary therapies used in many types of cancer include aromatherapy, massage, meditation, music therapy, prayer, and certain forms of exercise. These therapies have the objective of reducing anxiety and increasing a patient's feeling of well-being.

Numerous alternative therapies exist in cancer treatment. Plant extracts, **vitamins**, protein therapies, and natural substances such as mistletoe and shark cartilage have all been touted as cancer-fighting remedies. However, some alternative therapies, such as Laetrile, can produce dangerous side effects and have shown no anticancer activity in **clinical trials**. Patients interested in alternative therapies should consult their doctors to ensure that the products are safe, especially for children, and do not interfere with regular cancer treatment.

Coping with cancer treatment

During treatment, a child's health will be followed by the team of physicians involved. Those physicians will be able to monitor the child for any side effects from the treatments, especially if the child is receiving chemotherapy. The most frequent side effects of chemotherapy can include nausea and vomiting, **diarrhea**, **fatigue**, and hair loss (alopecia). With medications, physicians can often treat some of the side effects, especially nausea, vomiting, and diarrhea.

Cancer treatment can be especially frightening for a young child. Family support is critical, and parents should consult their physicians about any organizations in the area that can help their child cope with the effects of medulloblastoma and its treatment.



Colorized three-dimensional computed tomography brain scan showing a medulloblastoma tumor (red). *(Copyright CNRI/Science Photo Library, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Clinical trials

There are many clinical trials being done to help better the treatment options for medulloblastoma. Some of the most promising ones are studies in which peripheral stem cell transplantation is used. This is a technique in which certain cells in the body known as stem cells are used to replace other, depleted cells, such as the immune cells and blood cells that are destroyed when chemotherapy is used. It is hoped that with stem cell use, physicians will be able to use higher doses of chemotherapy in order to destroy the medulloblastoma cancer.

Prevention

There are currently no known ways to prevent medulloblastoma. Those who have the very rare genetic disorders which predisposes them to medulloblastoma, Gorlin's and Turcot's syndrome, should be especially aware of any signs or symptoms of medulloblastomas. Children of parents with these genetic disorders should have routine screening done by a pediatrician for any signs of a brain tumor.

See also Bone marrow transplantation; Childhood cancers.

Resources

BOOKS

Abeloff, Martin, James O. Armitage, Allen S. Lichter, and John E. Niederhuber. *Clinical Oncology*. New York: Churchill Livingstone, 2000.

ORGANIZATIONS

American Brain Tumor Association. Suite 146, 2720 River Rd., Des Plaines, IL 60018. (800) 886-2282. <http://www.abta.org>.

National Cancer Institute, National Institutes of Health. Building 31, Room 10A31, 31 Center Dr., MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. <http://www.nci.nih.gov>.

St. Jude Children's Research Hospital. 332 N. Lauderdale St., Memphis, TN 38105. (901) 495-3300. <http://www.stjude.org>.

OTHER

National Cancer Institute CancerTrials. [cited July 23, 2005]. <http://cancertrials.nci.nih.gov>.

Edward R. Rosick, D.O., M.P.H.

Megestrol acetate

Definition

Megestrol acetate is used to treat unexplained **weight loss** during cancer therapy and to stop new cell growth in some cancers. Megestrol acetate is also known by the brand name Megace.

Purpose

Megestrol acetate is used to treat some advanced hormone-responsive cancers of the breast, kidney, and uterus. It is also used in larger doses to help reverse weight loss for which there is no other treatable cause.

Description

Megestrol acetate is a synthetic derivative of the female hormone progesterone. In healthy women, progesterone plays a major role in preparing the uterus for pregnancy. It has been approved by the Food and Drug Administration (FDA), and its use is usually covered by insurance.

Exactly why megestrol acetate stops tumor growth is unclear. Many tumors are sensitive to hormones. It appears that megestrol acetate, in some way, changes the hormonal climate of the tumor so that cells stop responding to other hormones and proteins that would normally stimulate their growth. This drug cannot tell the difference between normal cells and cancer cells, so some normal cells are also killed during treatment. But since cancer cells grow more rapidly than normal cells, more cancer cells are killed.

Megestrol acetate has another independent use in cancer treatment. In high doses, it is used to counteract weight loss that does not occur for any other treatable reason. Megestrol acetate appears to bring about weight gain through increased fat storage.

Recommended dosage

Megestrol acetate comes in both liquid and tablet form. To treat weigh loss, the standard dosage is a single dose given in the morning with breakfast. Many clinical studies are underway to examine the best use of megestrol acetate in severe weight loss. Most of these studies are for people who are losing weight because they suffer with AIDS. However, the selection of **clinical trials** underway changes frequently. Current information on what clinical trials are available and where they are being held can be found by entering the search term "megestrol acetate" at the following websites:

- National Cancer Institute <http://cancertrials.nci.nih.gov> or (800) 4-CANCER
- National Institutes of Health Clinical Trials <http://clinicaltrials.gov>
- Center Watch: A Clinical Trials Listing <http://www.centerwatch.com>

To reduce tumor growth, the dose of megestrol acetate is individualized, and depends on the type of cancer, the patient's body weight and general health, what other drugs are being given, and the way the cancer responds to hormones. A standard dose of Megace to treat **breast cancer** is 160 mg/day divided into four doses. A standard dose for **endometrial cancer** (cancer of the uterus) is 40–320 mg/day in divided doses. Treatment normally continues for about two months.

Precautions

Women taking megestrol acetate should not get pregnant. Megestrol acetate is believed to cause birth defects in babies born to mothers who are taking the drug. A patient assistance program is available through Bristol Meyer Squibb, the manufacturer of this drug at (800) 332-2056.

KEY TERMS

Food and Drug Administration (FDA)—The government agency that oversees public safety in relation to drugs and medical devices, and gives the approval to pharmaceutical companies for commercial marketing of their products in the United States.

Hormone—A chemical released by a gland that travels through the circulatory system and affects only the tissues at a distance from its release point that have receptors for the chemical.

Progesterone—A female hormone that prepares the uterus for pregnancy.

Side effects

Megestrol acetate has several rare but serious side effects. Some people have been reported to develop **Cushing's syndrome**. This is a hormonal imbalance in which people (usually women) develop fatty deposits in the face and neck, lose bone mass (osteoporosis), stop menstruating, develop diabetes, high blood pressure, and other signs of fluid and salt (electrolyte) imbalances.

Other common side effects of megestrol acetate include:

- worsening of diabetic symptoms
- pain in the chest or abdomen
- infection
- sarcoma (tumors of the skin or connective tissue)
- irregular heartbeat
- fluid retention
- breakthrough vaginal bleeding
- blood clots in legs or lungs
- nausea or constipation
- dry mouth or increased salivation
- abnormal white blood cell count
- confusion or abnormal thinking
- emotional and psychological changes
- rash, **itching**, abnormal sweating, or skin disorders
- cough, sore throat, lung disorders
- hair loss (alopecia)
- uncontrolled urination or urinary tract infection
- male impotence

Interactions

No specific interactions with other pharmaceuticals have been reported in people using megestrol acetate. However, many drugs interact with nonprescription (over-the-counter) drugs and herbal remedies as well as prescription drugs. Patients should always tell their health care providers about all remedies they are taking. Patients should also mention if they are on a special diet such as low salt or high protein.

Tish Davidson, A.M.

Melanoma

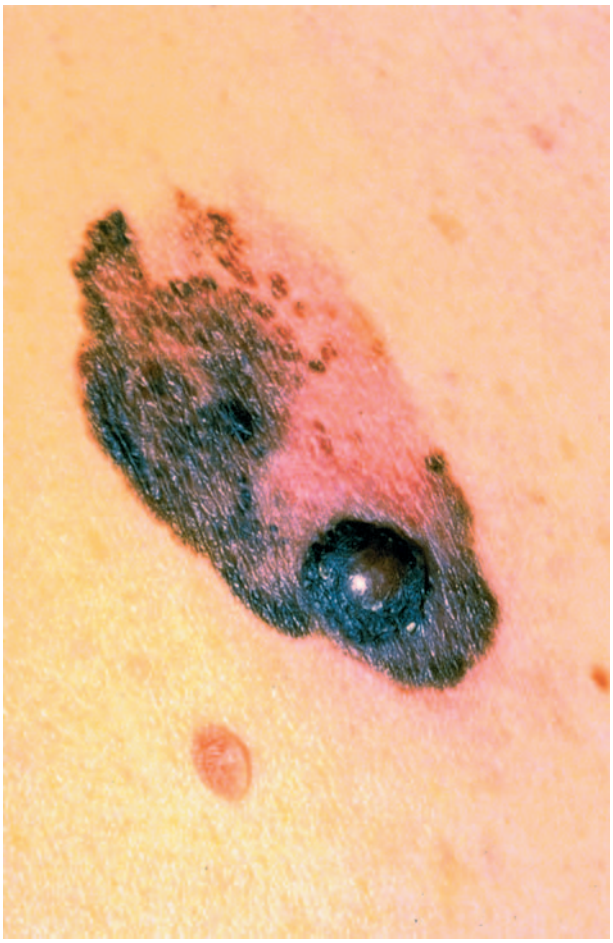
Definition

Malignant melanoma is a type of cancer arising from the melanocyte cells of the skin. The melanocytes are cells in the skin that produce the pigment melanin. Malignant melanoma develops when the melanocytes no longer respond to normal control mechanisms of cellular growth and are capable of invasion locally or spread to other organs in the body (**metastasis**), where again they invade and compromise the function of that organ.

Description

Melanocytes, embryologically derived from the neural crest, are distributed in the epidermis and thus are found throughout the skin. They produce a brown pigment known as melanin and are responsible for racial variation in skin color and also the color of moles. Malignant degeneration of the melanocyte gives rise to the tumor, melanoma, of which there are four subtypes. These are: superficial spreading, nodular, lentigo maligna, and acral lentiginous melanomas, accounting for 70%, 15% to 30%, 4% to 10%, and 2% to 8% of cases, respectively. Malignant melanoma may develop anywhere on the body. In men, it is most common on the trunk. In women, it is most common on the back or legs. The subtype also may influence where the tumor develops; lentigo melanoma is more common on the face while acral lentiginous melanoma is more common on the palms of the hand, soles of the feet, or in the nail beds.

The locally invasive characteristic of this tumor involves vertical penetration through the skin and into the dermis and subcutaneous (under-the-skin) tissues of the malignant melanocytes. With the exception of the nodular variety of melanoma, there is often a phase of



A close-up image of a malignant melanoma on a patient's back. *(Custom Medical Stock Photo. Reproduced by permission.)*

radial or lateral growth associated with these tumors. Since it is the vertical growth that characterizes the malignancy, the nodular variant of melanoma carries the worst prognosis. Fortunately, the superficial spreading type is most common.

The primary tumor begins in the skin, often from the melanocytes of a pre-existing mole. Once it becomes invasive, it may progress beyond the site of origin to the regional lymph nodes or travel to other organ systems in the body and become systemic in nature.

The lymph is the clear, protein-rich fluid that bathes the cells throughout our body. Lymph will work its way back to the bloodstream via small channels known as lymphatics. Along the way, the lymph is filtered through cellular stations known as nodes, thus they are called lymph nodes. Nearly all organs in the body have a primary lymph node group filtering the tissue fluid, or lymph, that comes from that organ. Different areas of the skin have different primary nodal stations. For the leg, they are in the groin. For the arm, the armpit or axilla. For the face, it is the neck. Depending where on the torso the tumor develops, it may drain into one groin or armpit, or both.

Cancer, as it invades in its place of origin, may also work its way into blood vessels. If this occurs, it provides yet another route for the cancer to spread to other organs of the body. When the cancer spreads elsewhere in the body, it has become systemic in extent and the tumor growing elsewhere is known as a metastasis.

Untreated, malignant melanoma follows a classic progression. It begins and grows locally, penetrating vertically. It may be carried via the lymph to the regional nodes, known as regional metastasis. It may go from the lymph to the bloodstream or penetrate blood vessels, directly allowing it a route to go elsewhere in the body. When systemic disease or distant metastasis occur, melanoma commonly involves the lung, brain, liver, or occasionally bone. The malignancy causes death when its uncontrolled growth compromises vital organ function.

Demographics

In the United States, malignant melanoma will account for 5% of malignancies in men and 4% in women, being the sixth most common cancer in men and the seventh in women. There will be 553,400 total cancer deaths in the United States. Malignant melanoma will account for 7,800 for an incidence of 1.5% of total deaths related to cancer.

The incidence of primary cutaneous malignant melanoma has been steadily increasing, possibly related to increase of sun exposure. Currently, the risk is about 13 per 100,000 of the population. It affects all age groups but is most commonly seen in patients between 30 and 60 years of age.

Sun exposure definitely increases risk of developing melanoma. The melanocytes are part of the integument's photoprotective mechanism; in response to sunlight, they produce melanin that has a protective role from the sun's ultraviolet rays. For Caucasians, the amount of melanin present in the skin is directly related to sun exposure. However, it is not so much the total sun exposure that seems important, rather it is the history of sunburn, (especially if severe or at an early age), that correlates with the increased risk. On this basis populations of fair-skinned people living in areas of high sun exposure such as the southwest United States or Australia are subject to increased risk. Malignant melanoma also affects non-Caucasians—though sun exposure probably does not

play a role—at a rate of 10% that of Caucasians. The most common form of melanoma in African Americans is acral lentiginous melanoma.

Malignant melanoma may arise in the skin anywhere on the body. It is estimated that 50% to 70% develop spontaneously while the remainder start in a pre-existing mole.

Causes and symptoms

The predisposing causes to the development of malignant melanoma are environmental and genetic. The environmental factor is excessive sun exposure. There are also genetically transmitted familial syndromes with alterations in the CDKN2A gene, which encodes for the tumor-suppressing proteins p16 and p19. In 2003, a group of Swedish researchers reported that 63 out of a group of 71 melanoma patients, or 89% of the group, had mutations in either the NRAS or the BRAF gene. The researchers found that these mutations occur at an early point in the development of melanoma and remain as the tumor progresses.

As of early 2003, some researchers think there may be two pathways to malignant melanoma, one involving exposure to sunlight and the other with melanocyte proliferation triggered by other factors. This hypothesis is based on the difference in distribution of moles on the body between patients who develop melanomas on the face and neck, and those who develop melanomas on the trunk.

A small percentage of melanomas arise within burn scar tissue. As of 2003, researchers do not fully understand the relationship between deep burns and an increased risk of skin cancer.

As mentioned previously, melanin production in fair-skinned people is induced by sun exposure. An exposure substantial enough to result in a mild sunburn will be followed by melanin producing a tan that may last a few weeks. Both ultraviolet radiation and damaging oxygen radicals caused by sun exposure may damage cells, particularly their DNA. It is suspected that this damage induces mutations that result in the development of malignant melanoma. Though these mutations are alterations of the genome causing the melanoma, they are environmentally induced and account for sporadic or spontaneous cases of this disease.

A positive family history of one or two first-degree relatives having had melanoma substantially increases the risk on a genetic basis. A family tendency is observed in 8% to 12% of patients. There is a syndrome known as the dysplastic (atypical) nevus syndrome that is characterized by atypical moles with bothersome clinical features in children under age 10. Such individuals have to be observed closely for the development of malignant melanoma. Chromosome 9p has been identified as being involved in familial predisposition. There are mutations in up to 50% of familial melanoma patients of the tumor-suppressing gene CDKN2A. The actual number of moles increases risk, but the size of the moles needs be considered. Those with 10 larger moles of over 1 cm (0.4 in.) are at more risk than those with a higher number (50–99) of smaller moles. Finally, when a child is born with a

KEY TERMS

Adjuvant therapy—Therapy administered to patients who are at risk of having microscopic untreated disease present but have no manifestations

Dermis—The deeper portion or layer of the skin

Dysplastic nevus syndrome—A familial syndrome characterized by the presence of multiple atypical appearing moles, often at a young age

Epidermis—The superficial layer of the skin

Genome—Composed of DNA, the genome is the genetic makeup of the cell

Immunotherapy—Therapy using biologic agents that either enhance or stimulate normal immune function

Integument—The skin

Lymph node dissection—Surgical removal of an anatomic group of lymph nodes

Lymphedema—Swelling of an extremity following surgical removal of the lymph nodes draining that extremity

Melanocyte—Cells derived from the neural crest that are in the skin and produce the protein pigment melanin

Metastasis—A tumor growth or deposit that has spread via lymph or blood to an area of the body remote from the primary tumor

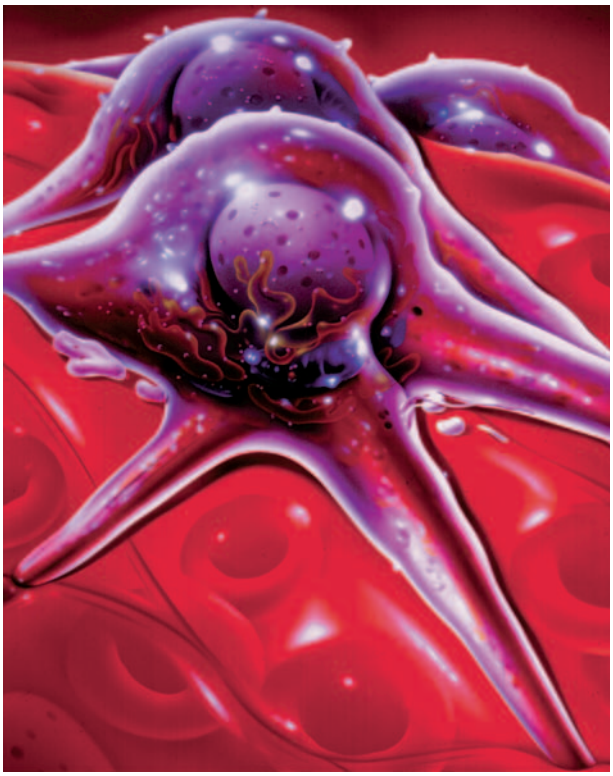
Nevus—A mole

Resection—The act of removing something surgically

Skin appendages—Structures related to the integument such as hair follicles and sweat glands

Systemic disease—Used to refer to a patient who has distant metastasis

Variegation—Patchy variation



Melanoma. *(Photo Researchers, Inc. Reproduced by permission.)*

large congenital mole, careful observation for change is appropriate because of increased risk.

An excellent way of identifying changes of significance in a mole is the ABCDE rule:

- Assymetry
- Border irregularity
- Color variegation
- Diameter exceeding 6 mm (0.24 in.)
- Elevation above surrounding tissue.

Notice that three of the criteria refer to variability of the lesion (color variegation refers to areas of light color and black scattered within the mole). Thus small, uniform regular lesions have less cause for concern. It is important to realize that change in a mole or the rapid development of a new one are very important symptoms.

Another summary of important changes in a mole is the Glasgow 7-point scale. The symptoms and signs below can occur anywhere on the skin, including the palms of the hands, soles of the feet, and also the nail beds:

- change in size
- change in shape
- change in color
- inflammation
- crusting and bleeding
- sensory change
- diameter more than 7 mm (0.28 in.)

In this scheme, change is emphasized along with size. Bleeding and sensory changes are relatively late symptoms.

Symptoms related to the presence of regional disease are mostly those of nodules or lumps in the areas containing the lymph nodes draining the area. Thus nodularity can be found in the armpit, the groin, or the neck if regional nodes are involved. There is also a special type of metastasis that can occur regionally with malignant melanoma; it is known as an in-transit metastasis. If the melanoma is spreading through the lymph system, some of the tumor may grow there, resulting in a nodule part way between the **primary site** and the original lymph node. These in-transit metastasis are seen both at the time of original presentation or later after primary treatment has been rendered, the latter being a type of recurrence.

Finally, in those who either are diagnosed with or progress to widespread or systemic disease, symptoms and signs are related to the affected organ. Thus neurologic problems, lung problems, or liver problems develop depending on the organ involved.

Diagnosis

None of the clinical signs or symptoms discussed above are absolute indications that a patient has malignant melanoma. The actual diagnosis is accomplished by **biopsy**, a procedure that removes tissue to examine under a microscope. It is important that the signs and symptoms are used to develop a suspicion of the diagnosis because the way the biopsy is performed for melanoma may be different than for other lesions of the skin.

When dealing with an early malignant melanoma, it is very important to establish the exact thickness of penetration of the primary tumor. Any biopsy that doesn't remove the full vertical extent of the primary is inadequate. Therefore, if a skin lesion is suspicious, full thickness excisional biopsy is the approach recommended. Shave biopsies and biopsies that remove only a portion of the suspect area are inappropriate. Often, in an early case, the excision involves just the suspicious lesion with minimal normal skin, but it should be a full vertical excision of the skin. If a melanoma is diagnosed, further treatment of this area will often be necessary but doesn't compromise outcome (prognosis). In some special areas of the body, minor modifications may be nec-

essary about initial total excision, but full thickness excision should always be the goal. (See staging, below.)

Once the diagnosis is obtained, careful examination of the patient for regional lymph node involvement should be done. A careful review to uncover any symptoms of widespread disease is also appropriate.

The more common patient has an early melanoma, and extensive testing is not usually warranted. Routine testing in this situation involves a complete blood count, a chest **x ray**, and determinations of blood enzymes including lactic dehydrogenase and alkaline phosphatase.

If the patient has signs or symptoms of more advanced disease, or if the lesion's depth of penetration is sizeable, further **imaging studies** may be appropriate. These would involve CAT scans of the abdomen, the chest, or regional nodal areas, or a CT or MRI of the brain.

Treatment team

The treatment of malignant melanoma is primarily surgical. Newer, more effective protocols involving the medical oncologist are being developed for the patient with systemic disease. **Radiation therapy** has a limited role in the treatment of melanoma, primarily that of helping to ease the effects of metastasis to the brain or sometimes the skeleton.

Clinical staging, treatments, and prognosis

The key to successful treatment is early diagnosis. Patients identified with localized, thin, small lesions (typified by superficial spreading subtype) nearly always survive. For those with advanced lesions, the outcome is poor in spite of progress in systemic therapy.

Clinical staging

Malignant melanoma is locally staged based on the depth of penetration through the skin and its appendages. There are two ways of looking at the depth of penetration. The Clarke system utilizes the layers of the dermis and the skin appendages present at that layer to identify the depth of penetration. The Breslow system uses the absolute measurement of depth. Though useful conceptually, the Clarke system is used less frequently because of the fact that skin is of different thickness in different regions of the body. The depth of penetration is much greater when the tumor reaches the subcutaneous fat when the skin involved is the back as opposed to the face. It turns out that the Breslow measurement is more reproducible and thus more useful; therefore, for purposes here, depth of penetration by absolute measurement (Breslow) is used in local staging.

Stage I and stage II have no involvement of the regional lymph nodes and are thus localized to the site of origin. These stages are subdivided on the basis of penetration. Stage Ia is 0.75 mm or less (1 mm = 0.04 in), and Stage Ib is 0.75 mm to 1.5 mm penetration. Stage IIa is 1.5 mm to 4.0 mm and Stage IIb is over 4.0 mm or into the subcutaneous fat. In stage III and IV, there is disease beyond the primary site. Stage III is defined by the presence of in-transit or regional nodal metastasis or both. Stage IV is defined by the presence of distant metastasis.

Treatments

Once the diagnosis of malignant melanoma has been established by biopsy and the stage has been identified using the results of the examination and studies, a treatment plan is developed. Melanoma is not cured unless it is diagnosed at a stage when it can be isolated and removed surgically. Considerations revolve around the extent of the local and regional nodal surgery for stages I through III. For stage IV patients, or those that are treated and then develop recurrence at distant sites, **chemotherapy** or immunotherapy is planned. Studies are in progress to improve the results from traditional chemotherapeutic regimens. Adjuvant therapy (auxiliary drug treatment used to make possibility of relapse less for those at high risk) is also considered.

Surgical therapy for the primary site is that of wide local removal of the skin including subcutaneous tissue surrounding the lesion. In the past, wide excisions were large and encompassed 2 in. of tissue in all directions wherever feasible. It has been shown that such wide local excisions are not necessary and the question has become how wide is necessary? Studies from the World Health Organization Melanoma Group and by the Melanoma Intergroup Committee in the United States have provided general guidelines based on the depth of penetration of the melanoma. These guidelines and anatomic considerations need to be kept in mind by the surgeon.

The next issue in primary management is whether or not the patient needs to have the regional lymph nodes removed in addition to treatment of the primary tumor. The problems associated with the resection of regional lymph nodes are those of lifelong edema or swelling in the extremity. Though it does not occur in all patients (5% to 20%, depending on the extremity and extent of the dissection), it can be a disabling symptom. Certainly, if it could be ascertained that there was disease in the nodes, resection (removal) would be appropriate. However, if there was no disease, the risk of edema should be avoided. In patients with no signs of regional disease, depth of penetration of the primary tumor helps guide the decision. If the tumor penetrates less than 1mm, dissection is not

usually done. If it is 1-2 mm, node dissection may be done at the time of primary treatment or the patient may be observed and only undergo **lymph node dissection** if the area later shows signs of disease. If the patient has enlarged lymph nodes or the depth of the tumor has led to the evaluation by CAT scan showing enlarged nodes, resection of the nodes will be considered. In the latter case, more extensive imaging of the lung, liver, or brain may be appropriate to be sure the patient doesn't already have stage IV disease.

Questions related to which patients should have resection of regional lymph nodes have led to an intermediary procedure known as sentinel lymph node mapping and biopsy. Intermediate thickness melanomas between 1 and 4 mm deep (0.04 and 0.16 in.) may have nodal involvement even if the exam and any other studies done are normal. If a radioisotope tracer or blue dye is injected into the area of the primary tumor, very shortly it will travel to the lymph nodes draining that area. These sentinel nodes are thus identifiable and are the most likely to harbor any regional metastatic disease. If these nodes alone are biopsied and are normal, the rest of the lymph node group can be spared. If they show microscopic deposits of tumor, then the full resection of the lymph node group may be completed. This procedure allows selection of those patients with intermediate thickness melanoma who will benefit from the regional lymph node dissection.

Patients with metastatic melanoma who do not respond well to other therapies may be candidates for treatment with **aldesleukin** (also called interleukin-2), a specific kind of biological response modifier that promotes the development of T cells. These cells are part of the lymphatic system and can directly interact with and fight cancer cells. Although interleukin is produced naturally in the body, its therapeutic form is developed via biotechnology in a laboratory setting. In some patients, this medication has helped shrink tumors. Side effects, however, can be severe, and range from flu-like symptoms to whole-body infection (sepsis) and coma.

Some patients, such as those with IIb or stage III melanoma, are at high risk for the development of recurrence after treatment. Although these patients are clinically free of disease after undergoing primary treatment, they are more likely to have some microscopic disease in the body that studies have not yet been able to identify. In an effort to decrease the rate of relapse, adjuvant therapy may be considered. Interferon alpha 2a is an agent that stimulates the immune system. This adjuvant therapy may slightly increase the duration of a patient's disease-free state and lengthen overall survival. However, interferon alpha 2a has high toxicity and patients may not tolerate the side effects.

Unfortunately, treatment for those patients who present with or go on to develop systemic disease usually fails; melanoma that has metastasized to the brain is particularly difficult to treat. The chemotherapeutic agent **dacarbazine**, or DTIC, seems to be the most active agent. Overall responses are noted in about 20% of patients, and they last only two to six months. Combination therapy may be an option. The regimen of DTIC + BCNU (**carmustine**) + **cisplatin** + **tamoxifen** delivers a response rate of 40%. Combining biologic or immunologic agents such as interferon with standard chemotherapeutic agents is under study and showing improved response rates, though toxicity is substantial and only the healthier, younger patients tolerate the treatment.

Some researchers are investigating the reasons why melanomas are so resistant to chemotherapy. One suggestion as of late 2003 is that the genes ordinarily responsible for apoptosis (cell self-destruction) do not function normally in melanomas. The development of new drugs to treat melanoma depends on a better understanding of the complex processes involved in apoptosis.

Prognosis

Almost all patients survive stage Ia malignant melanoma, and the suvivorship for stage I overall is more than 90%. Survival drops in stage IIa to about 65% at five years and is worse yet for stage IIb at slightly over 50%. Stage III has a survival rate at 5 years of 10% to 47%, depending on the size and number of regional nodes involved. Stage IV malignant melanoma is almost always a fatal disease.

Alternative and complementary therapies

Though radiation therapy has a minimal role in the primary treatment of malignant melanoma, for patients who have metastatic disease, radiation may be helpful. This is true in patients who have developed tumor deposits in areas such as the brain or the bone.

Coping with cancer treatment

For those with familial tendencies for malignant melanoma, genetic counseling may be appropriate. Psychological counseling may be appropriate for anyone having trouble coping with a potentially fatal disease. Local cancer support groups may be helpful and are often identified by contacting local hospitals or the American Cancer Society.

Clinical trials

Clinical trials are studies of new modes of therapy in an effort to improve results of treatment. For those

QUESTIONS TO ASK THE DOCTOR

- What stage of cancer do I have?
- Has the cancer spread? What tests will be used to determine this?
- What are my treatment options?
- Is adjuvant therapy really necessary in my case?
- What are the risks and side effects of these treatments?
- What medications can I take to relieve treatment side effects?
- Are there any clinical studies underway that would be appropriate for me?
- What effective alternative or complementary treatments are available for this type of cancer?
- How debilitating is the treatment? Will I be able to continue working?
- How will the treatment affect my sexuality?
- Are there any local support groups for melanoma patients?
- What is the chance that the cancer will recur?
- Is there anything I can do to prevent recurrence?
- How often will I have follow-up examinations?

wishing to find a trial related to their particular situation, the National Cancer Institute lists those available at: <http://cancernet.nci.nih.gov/trialsrch.shtml>.

In an attempt to develop a new type of immunotherapy, melanoma-specific **vaccines** are being developed. Antigens specific to melanoma cells and other tumor-associated antigens are being used to stimulate the body's own natural immune system to attack and kill the cells of malignant melanoma. Though experimental, this type of therapy offers hope and clinical trials are underway. In 2003 a team of researchers in New York reported that vaccines made from poxviruses show promise as a treatment for melanoma.

Prevention

Though it is difficult to prove that sunscreens statistically reduce the frequency of malignant melanoma at this time, most authorities recommend use as protection from ultraviolet light (considered a major factor in the development of melanoma.) Avoidance of severe sunburns is recommended.

Special concerns

Sub-ungal melanoma is a type of acral lentiginous melanoma that occurs in the nail beds. Any pigmented lesion in these areas needs evaluation. They are commonly mistaken for bruises or infection. The main concern is to know they exist so that proper evaluation is performed as early as possible.

Malignant melanoma may also involve the eye, as melanin-producing cells exist there also. Again, familiarity with these spots is important so that pigmented growths are not ignored but evaluated early.

Rarely, a patient presents with regional lymph node involvement, but the primary site of the tumor cannot be identified. The primary may not be producing pigment and is known as an amelanonic melanoma. Because these patients present with stage III disease, they do less well as a group overall.

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Melphalan

Definition

Melphalan is an anticancer (antineoplastic) agent. It also acts as a suppressor of the immune system. It is available under the brand name Alkeran.

Purpose

Melphalan is primarily used to treat **ovarian cancer** and **multiple myeloma**, which is a type of cancer of the bone marrow. It is also used to treat cancers that have metastasized to the liver.

Although not specifically labeled for use in the treatment of these cancers, melphalan is also used in some patients with:

- breast cancer
- cancers of the blood and lymph system
- endometrial cancer
- malignant melanoma
- Waldenström's macroglobulinemia

More recently, melphalan has been used to prevent rejection of transplanted stem cells in the treatment of metastatic breast cancer and renal cell carcinoma.

Description

Melphalan is a nitrogen mustard derivative and belongs to the group of alkylating anticancer agents. It chemically interferes with the synthesis of genetic material (DNA and RNA) of cancer cells, which prevents these cells from being able to reproduce and continue the growth of the cancer.

Recommended dosage

Melphalan may be taken either orally in pill form or as an injection in liquid form. The dosage prescribed may vary widely depending on the patient, the cancer being treated, and whether or not other medications are also being taken.

A typical dosage for multiple myeloma is 6 mg per day for two to three weeks. After this initial dose, the drug is halted for up to 4 weeks, then resumed at a dose of 2 mg per day, depending on blood counts of the drug in the patient's blood test.

A typical dosage for ovarian cancer is 0.2 mg per kilogram (2.2 pounds) of body weight once per day for five days.

Precautions

Melphalan should be taken with food to minimize stomach upset. Melphalan should always be taken with plenty of fluids.

Melphalan can cause an allergic reaction in some people. Patients with a prior allergic reaction to melphalan should not take the drug.

KEY TERMS

Antineoplastic—A drug that prevents the growth of a neoplasm by interfering with the maturation or proliferation of the cells of the neoplasm.

Neoplasm—New abnormal growth of tissue.

Melphalan can cause serious birth defects if either the man or the woman is taking this drug at the time of conception, or if the woman is taking this drug during pregnancy. Also, male sterility is a possible side effect of melphalan. This sterility may either be temporary or permanent.

Because melphalan is easily passed from mother to child through breast milk, breastfeeding is not recommended while melphalan is being taken.

Melphalan suppresses the immune system and interferes with the normal functioning of certain organs and tissues. For these reasons, it is important that the prescribing physician is aware of any of the following preexisting medical conditions:

- a current case of, or recent exposure to, chicken pox
- herpes zoster (shingles)
- a current case, or history of, gout or kidney stones
- all current infections
- kidney disease

Because melphalan is such a potent immunosuppressant, patients taking this drug must exercise extreme caution to avoid contracting any new infections. They should do their best to:

- avoid any person with any type of infection
- avoid any person who has received a polio vaccine in the last two months
- avoid bleeding injuries, including those caused by brushing or flossing the teeth
- avoid contact of the hands with the eyes or nasal passages unless the hands have just been washed and have not touched anything else since this washing
- avoid contact sports or any other activity that could cause a bruising or bleeding injury

Side effects

There are no common side effects of melphalan. Side effects that may occur, however, include:

- increased susceptibility to infection
- nausea and vomiting
- diarrhea
- mouth sores
- skin rash, **itching**, or hives
- swelling in the feet or lower legs

A doctor should be consulted immediately if the patient experiences black, tarry, or bloody stools, blood in the urine, persistent cough, **fever** and chills, pain in the lower back or sides, painful or difficult urination, or unusual bleeding or bruising.

Interactions

Melphalan should not be taken in combination with any prescription drug, over-the-counter drug, or herbal remedy without prior consultation with a physician. It is particularly important that the prescribing physician be aware of the use of any of the following drugs:

- amphotericin B
- antithyroid agents
- azathioprine
- chloramphenicol
- colchicine
- flucytosine
- ganciclovir
- interferons
- plicamycin
- probenecid
- sulfinpyrazone
- zidovudine
- any **radiation therapy** or **chemotherapy** medicines

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Memory change

Description

Many people with cancer experience memory changes—such as mild forgetfulness, an inability to concentrate on more than one task, or more severe memory loss—after undergoing **chemotherapy** or radiation treatments. In other cases, as in a person with a brain tumor, the cancer itself may cause memory changes. Surgical interventions, particularly for brain cancer, may also lead to memory loss.

Causes

Studies show that patients experience trouble with memory and language skills after chemotherapy. Scientists are searching for the exact cause, but they believe the chemotherapy agents may be associated with this side effect. The drugs are designed to attack cancer cells, but often kill healthy cells in the process. Researchers are studying whether chemotherapy agents may be damaging healthy brain cells. Others believe the cancer itself may be responsible for the memory changes.

Similarly, **radiation therapy** also may cause people with cancer to lose some mental abilities, including memory. Physicians use radiation waves to penetrate cancer cells and stop them from growing. During the process, the rays may damage some healthy tissue. The severity of damage depends on the dose and duration of the radiation treatments. In some cases, cells killed by radiation can form a tumor-like mass in the brain, which can lead to memory loss. Children who undergo radiation treatments for a brain tumor may have developmental delays later in life.

Other side effects of cancer, such as **fatigue**, pain, and **depression**, may lead to memory impairment as a person struggles to cope with cancer. Living with constant pain, for example, takes a great deal of energy and can cause a person to become more distracted than usual. Sometimes, especially in elderly patients, it can be difficult to tell if the memory changes are caused by an existing dementia or the cancer treatment.

Treatments

Depending on the type and intensity of cancer treatment, memory difficulties may fade over time. Some people, however, will experience a permanent loss. Families can help by offering useful strategies, such as making lists of daily tasks, using a calendar or daily organizer, reducing stress, and encouraging the person to ask for help if disoriented.

Patients scheduled for radiation therapy should discuss their concerns about memory loss with their physician before the treatment begins. The radiologists may be able to control the dosage to minimize damage to healthy cells. For instance, many hospitals use a gamma knife for brain cancer treatment. The device allows radiation therapists to simultaneously attack a tumor with high-energy rays from several different angles. The gamma knife sends a concentrated dose to the tumor without damaging surrounding brain tissue.

Occupational therapists can assist people who find that cancer-related memory changes are interfering with their ability to work or perform normal activities. Many people learn helpful coping strategies from other cancer survivors by joining a support group. Since more damage occurs in younger patients, children who go through radiation therapy for brain tumors may need extra tutoring, or special education programs when they go to school.

Alternative and complementary therapies

Often, when physicians prescribe medication to ease a person's pain or depression, the patient's memory may improve as well. Researchers also are studying the ability of the herb *gingko biloba* to increase mental sharpness. Although it has not yet been proven to be completely effective, some people with memory loss find it helpful. Since gingko can cause circulatory problems, it is important to check with a doctor before taking it.

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Memory loss *see* **Memory change**

Meningioma

Definition

A meningioma is a benign tumor of the central nervous system that develops from cells of the meninges, the membranes that cover and protect the brain and spinal cord.

Description

The meninges

The delicate tissues of the brain and spinal cord are protected by a layer of bone and an inner covering called the meninges. The meninges are composed of three layers:

- dura mater
- arachnoid
- pia mater

The tough, thick dura mater forms the outer layer of the meninges and is attached to the bone of the skull and spinal cord. The arachnoid and pia mater layers are thinner and more delicate than the dura mater. The innermost pia mater layer is attached directly to the brain and spinal cord. Meningiomas arise from the middle arachnoid layer, and most remain attached to the dura mater by a dural tail.

Types of meningiomas

Meningiomas account for 15–20% of all brain tumors, and 25% of all spinal cord tumors. The World Health Organization (WHO) classifies meningiomas into 11 different categories according to their cell type. However, because there are so many different cell types and so much overlap between types, meningiomas are most often placed into three general categories, including benign, atypical, and malignant.

Benign meningiomas are by far the most common, accounting for more than 90% of all meningiomas. These tumors grow slowly and produce symptoms only if they become large enough to compress nearby brain tissue. In some patients, meningiomas can grow very large with almost no symptoms. This happens because the tumor has grown very slowly and has gradually compressed the brain over time. Meningiomas can also cause fluid to build up in the brain, and can sometimes block veins. They may also grow into nearby bone, causing the bone to become thicker.

Up to 7% of meningiomas are classified as atypical. These tumors grow more quickly than benign meningiomas and are more likely to be symptomatic. Malignant meningiomas are fast-growing aggressive tumors and are the most rare, accounting for only about 2% of all meningiomas. It is extremely unusual for meningiomas to metastasize to other organs. When they do, the lungs are the most common site.

Only about one tenth of meningiomas are found in the spine. These slow-growing tumors cause symptoms when they begin to compress the spinal cord. Spinal meningiomas usually grow in the spinal canal between the neck and the abdomen, and are almost always benign.

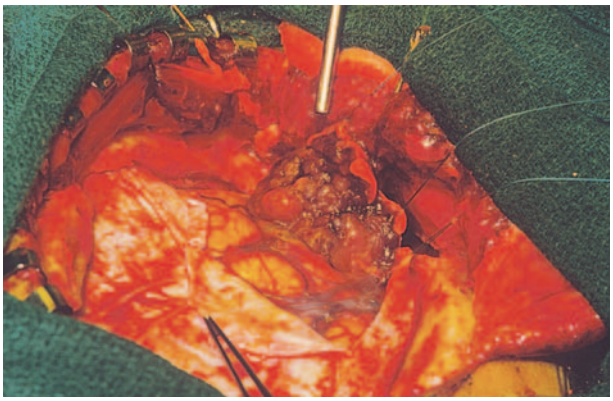
Demographics

Only one person in every 50,000 is diagnosed with a symptomatic meningioma annually. Most of these patients are women. Women develop brain meningiomas almost twice as often as men and spinal meningiomas four to five times more often than men. The disease usually strikes middle-aged and elderly patients. Men are most affected between the ages of 50 and 60 years, while women are most affected between the ages of 60 and 70 years. Atypical and malignant meningiomas are more common in men. Meningiomas do not occur very often in children.

Causes and symptoms

Causes

Although no single factor has been found that causes meningiomas, several risk factors are known. Some patients have developed a meningioma after being exposed to radiation. These patients tend to be younger than typical meningioma patients, and their tumors often grow more quickly. According to one study, the average age of patients with radiation-induced meningiomas is 38 years.



Brain surgery to remove an invasive meningioma. *(Custom Medical Stock Photo. Reproduced by permission.)*

There is also a genetic component to meningioma. Patients who suffer from neurofibromatosis, a rare genetic disease, often develop multiple meningiomas.

Since meningioma cells recognize the female sex hormone progesterone, some researchers believe that female sex hormones may play a role in the development of meningiomas. This possible link is still being investigated.

A group of researchers at the National Cancer Institute reported in 2004 that people in certain occupations have a higher than normal risk of developing meningiomas. These higher-risk occupations include auto body painting, industrial production supervision, teaching, business management, interior decorating and design, and career military service. Further research is needed to determine whether there is a common causal factor linking these different fields of work.

Symptoms

Up to 75% of meningiomas produce no symptoms because they grow slowly and remain small. Often, tumors are discovered only when patients are being investigated for an unrelated illness. When symptoms do appear, it results that the tumor has grown large enough to compress part of the brain or spinal cord.

Patients experience different symptoms depending on the location of the tumor. Most brain meningiomas are located either just below the top of the skull, or between the two hemispheres of the brain. If the tumor is located in these areas, symptoms include:

- headaches
- seizures
- dizziness
- problems with memory
- behavior changes
- protrusion of one or both eyeballs (exophthalmos)

More rarely, tumors are near sensory areas of the brain such as the optic nerve or close to the ears. Patients with these tumors experience vision or hearing losses.

Spinal meningiomas are usually found in the spinal column between the neck and the abdomen. The most common symptoms are:

- pain
- weakness and stiffness of the arms and legs
- episodes of partial paralysis

Diagnosis

Meningiomas are diagnosed using a painless noninvasive technique called **magnetic resonance imaging** (MRI). MRI works by exposing the patient to harmless radio waves and a magnetic field, which produce clear images of the brain and the spine that show the size and location of tumors. No special preparation is required for the test.

Diagnosis can also be made by **computed tomography** (CT) scan. The CT scan uses low-dose x rays to generate a picture of the inside of the body. Sometimes a dye is injected into the patient's vein to improve the visibility of tissues. If the meningioma has grown into nearby bone, a CT scan will show the extent of bone invasion better than MRI. Women who are pregnant, or who think they might be pregnant, should tell their doctors before having a CT scan.

Treatment team

The treatment team for a patient with a symptomatic meningioma may include a radiologist, a neurologist (specialist of the nervous system), and a neurosurgeon.

If surgery is necessary, a neurosurgeon will perform the procedure with the help of a surgical team. The team includes two or three nurses, and an anesthesiologist.

A small number of patients receive radiotherapy for their meningioma either because the tumor is too difficult to remove surgically, or because the surgeon had to leave some tumor behind. These patients will be referred to a radiation oncologist (specialist in giving radiation to cancer patients).

Clinical staging, treatments, and prognosis

Staging

Meningiomas are classified into three different grades depending upon the likelihood of recurrence and aggressive growth:

KEY TERMS

Benign tumor—A growth that is non-cancerous.

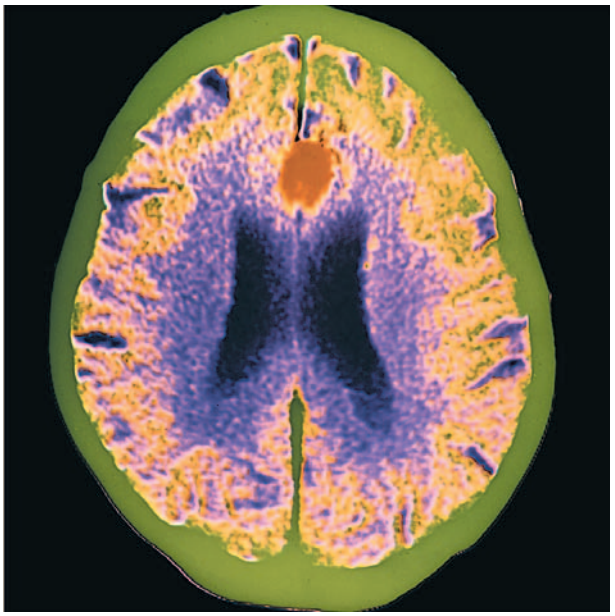
Computed tomography (CT) scan—A method of imaging the inside of the body using x rays.

Magnetic resonance imaging (MRI)—A method of imaging the inside of the body using radio waves and a magnetic field.

Meninges—Membranes that cover and protect both the brain and spinal cord.

Neurofibromatosis—A rare, genetic disease that causes tumors to grow in the nervous system.

Radiotherapy—The use of radiation to treat a medical condition.



Colored computed tomography (CT) scan of the brain showing a meningioma. At upper center is the tumor (red). The cerebrum is colored yellow and light purple. *(Copyright Department of Clinical Radiology, Salisbury District Hospital, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

- Grade I: Low risk of recurrence and slow growth
- Grade II: Greater likelihood of recurrence and/or aggressive growth
- Grade III: High recurrence rates and aggressive growth.

The vast majority of meningiomas are grade I. Atypical tumors are grade II, and malignant tumors are grade III.

Medical therapies

Medical treatment for meningiomas is necessary when tumors cause symptoms. Fortunately, only about a quarter of meningiomas become symptomatic. Most patients are cured by surgery.

The objective of surgery is to remove not only the entire meningioma, but also the tail that attaches the tumor to the meninges. If the tumor has grown into bone, the bone is removed, too. If the tumor is in a difficult location in the brain, the surgeon may leave some tumor behind in order to preserve brain tissue.

The prognosis following brain meningioma treatment is very good. For the few patients who are not cured, prognosis depends on how completely the tumor is removed. If some tumor is left behind, recurrence is more likely, particularly for patients with grade II or grade III meningiomas. Ten years after surgery, 7–20% of patients with benign grade I tumors have a recurrence. For patients with malignant grade III tumors, up to 78% have a recurrence. A second surgery is sometimes necessary for patients with recurrent tumors.

Spinal meningioma is the most successfully treated meningioma, and the most successfully treated of all spinal tumors. Most of these tumors are removed completely, and they rarely recur. Even patients with quite severe symptoms fully recover after surgery.

For the few patients who are inoperable (usually because of tumor location), **radiation therapy** can stop the growth of tumors. Recently, stereotactic radiosurgery has been successfully used. This procedure uses images of the patient's skull to construct a frame that allows precise aiming of radiation, thus minimizing harm to nearby healthy tissue. Another option is fractionated radiotherapy, which also delivers precise doses of radiation to very small areas of tissue.

Not every patient with a meningioma receives surgery or radiation. Asymptomatic patients with small or slow-growing tumors can receive periodic MRI tests to check tumor growth. Treatment may also not be necessary for patients with mild or minimal symptoms.

Alternative and complementary therapies

Unlike many other cancers, conventional medical treatment of meningioma has very high success rates. As a result, alternative therapies are not commonly used for these tumors.

QUESTIONS TO ASK THE DOCTOR

- Will I need to have surgery?
- Can I expect a full recovery after surgery?
- Will I need radiotherapy?
- How often will I need to return for an MRI or CT scan?
- How soon can I return to work after surgery?

Coping with cancer treatment

When first diagnosed with a meningioma, many patients experience anxiety, resulting in nervousness, sleepless nights, and even nausea. However, patients can often relieve many of their fears by learning more about the disease and its course of treatment. Nevertheless, about 21% of patients with meningiomas develop psychiatric disorders, most commonly depression or an anxiety disorder.

The majority of meningioma patients are treated with surgery alone. Surgery will involve a hospital stay of at least a week. Before going home, patients are usually given medications to help prevent pain and swelling. Once home, patients can expect to feel some headache pain, and will become tired easily. If headaches and weakness become worse, a doctor should be contacted. Patients should make sure they get plenty of rest and eat a balanced, nutritious diet. Most patients can begin to resume their normal activities in about six to eight weeks.

Clinical trials

Chemotherapy is seldom given to meningioma patients because surgery (and/or radiotherapy) is usually successful. For patients with tumors that do not respond to these treatments, however, chemotherapy is available within a clinical trial.

Clinical trials have investigated several drugs to treat patients whose meningioma recurs following failure of both surgery and radiotherapy. **Hydroxyurea**, a drug used to treat some other cancers, has been shown to slow the growth of meningioma cells. Studies of hydroxyurea continue. Some trials have explored the link between meningioma and female sex hormones. **Tamoxifen**, an anti-estrogen drug used to fight **breast cancer**, has produced disappointing results. Trials using RU-486, an anti-progesterone agent, are underway. Information on these and other open clinical trials is available on the Internet from the National Cancer Institute at <http://www.nci.nih.gov>.

Prevention

The most avoidable risk factor for the development of meningioma is exposure to radiation. Children exposed to small amounts of radiation in the 1950s to treat tinea captis, a fungal infection of the scalp, developed meningiomas at an unusually high rate. There is also a clear relationship between radiation dose and meningioma: the higher the radiation dose, the greater the probability of developing a meningioma.

Special concerns

The very elderly

In very elderly people, the symptoms of a meningioma can be very similar to normal aging. These patients typically experience difficulty with learning and remembering things as a result of the tumor. Headaches, a classic symptom of a meningioma, are not usually reported. Treatment of very elderly patients may be difficult if the patient is too frail for surgery.

Children

On the rare occasions that meningiomas are diagnosed in children, they tend to be large, fast growing, and located in unusual positions. Treatment for children is the same as for adults: complete tumor removal with surgery and/or radiotherapy.

Neurofibromatosis

Neurofibromatosis (NF) is actually two different genetic diseases: NF Type 1 and NF Type 2. NF Type 2 is the more rare of the two diseases, affecting only one in 40,000 individuals. These patients often develop multiple brain meningiomas. Although there is no cure for NF, meningioma tumors can be removed with surgery.

Resources

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Yamasaki, Fumiyuki, et al. "Recurrence of Meningiomas." *Cancer* 89, no. 5 (September 1, 2000): 1102–1110.

ORGANIZATIONS

American Brain Tumor Association. 2720 River Road, Des Plaines, IL 60018. (800) 886-2282. <http://abta.org>.

The Brain Tumor Society. 124 Watertown Street, Suite 3-H, Watertown, MA 02472. (800) 770-8287. <http://www.tbts.org>.

The Johns Hopkins Meningioma Society. Johns Hopkins University. Harvey 811, 600 North Wolfe Street, Baltimore, MD 21205-8811. (410) 614-2886. <http://www.meningioma.org>.

National Brain Tumor Foundation. 414 Thirteenth Street, Suite 700, Oakland, CA 94612-2603. (800) 934-2873. <http://www.braintumor.org>.

National Cancer Institute (National Institutes of Health). 9000 Rockville Pike, Bethesda, MD 20892. (800) 422-6237. <http://www.nci.nih.gov>.

Alison McTavish, M.Sc.
Rebecca J. Frey, Ph.D.

MENS, MEN syndrome *see* **Multiple endocrine neoplasia syndromes**

Meperidine

Definition

Meperidine, available as hydrochloride salt, is a narcotic analgesic, a classification term used to describe medications capable of producing a reversible **depression** of the central nervous system for pain control. Because of its potential for physical and psychological dependence, meperidine is a carefully controlled substance. It is commonly referred to by one of its brand names, Demerol.

Purpose

There are several possible indications for the administration of meperidine. It is commonly used for the relief of moderate to severe pain, particularly in obstetrics. Meperidine is also widely used preoperatively, and as an adjunct to anesthesia during surgery. Meperidine is not recommended for long-term management of chronic pain, such as pain caused by cancer, because of its potential for psychological and physical dependence.

Description

Meperidine is a synthetic compound that acts as an agonist—meaning it attaches to opioid receptors in the central nervous system and stimulates physiologic activity normally stimulated by naturally occurring substances such as endorphins (short for endogenous morphine). Meperidine acts much like morphine, although constipation, suppression of the cough reflex, and smooth muscle spasm are all reduced with meperidine.

Meperidine is available in a banana-flavored syrup, in a tablet, and in a liquid form for injection. Oral meperidine tends to be less effective than the injectable form. When taking the syrup, patients should dilute it with approximately one half glass of water to reduce temporary anesthesia to the mouth and tongue.

Recommended dosage

The recommended dosage of meperidine depends on the purpose for which it is prescribed, as well as the population in whom it is administered. For example, elderly patients, or patients with underlying medical problems that increase side effects or decrease drug metabolism, should generally be given reduced dosages. Meperidine can be taken orally, in tablet or syrup form, intravenously (directly into a vein), or by injection into the muscle (intramuscularly) or connective tissue (subcutaneously).

Generally, repeated doses administered to manage pain should be given by injection intramuscularly. The subcutaneous route is acceptable for occasional

KEY TERMS

Agonist—A drug that binds to cell receptors and stimulates activities normally stimulated by naturally occurring substances.

Endorphin—Short for endogenous morphine, it is a naturally occurring substance that binds to opioid receptors in the brain.

Narcotic analgesic—A classification of medications that relieves pain by temporarily depressing the central nervous system.

Opioid—A drug that possesses some properties characteristic of opiate narcotics but not derived from opium.

Patient controlled analgesic (PCA)—A device resembling an intravenous pump that allows patients to self-medicate within pre-established dosage parameters for pain control.

administration. When given intravenously, meperidine should be diluted and administered very slowly. When taken in conjunction with phenothiazine or other tranquilizers, the dose should be decreased by as much as a half. Specific dosages are as follows.

FOR RELIEF OF MODERATE TO SEVERE PAIN The recommended dosage for adults for pain relief is 50–150 mg every three to four hours by oral or intramuscular route. When given intravenously through a patient-controlled analgesia (PCA) device, an initial dose of 10 mg should be administered. The PCA should be programmed to administer between 1–5 mg every 6–10 minutes. If meperidine is given continuously through an intravenous line, the dose should be adjusted based on patient response to a range of 15–35 mg an hour. Children should be given 1–1.8 mg per kg (2.2 pounds) intramuscularly or subcutaneously.

FOR PREOPERATIVE MEDICATION Adults may be given 50–100 mg of meperidine intramuscularly, or subcutaneously 30–90 minutes prior to surgery. Children's dosages should be reduced to 1–2 mg per kg through the same routes.

For obstetric pain control. The recommended dosage for control of regular (not sporadic) pain in this setting is 50–100 mg every 1–3 hours intramuscularly or subcutaneously.

Precautions

Other patients who should avoid meperidine use include those with previous hypersensitivity to narcotics, or those with underlying respiratory problems. Meperidine, even in recommended therapeutic doses, can decrease the respiratory drive. Conditions such as asthma or chronic obstructive pulmonary disease may increase the likelihood of respiratory difficulty. Meperidine can also impair judgment, and should not be used in individuals engaging in activities that require alertness, such as driving.

Because its effects on a fetus are unknown, meperidine is not recommended in pre-labor stage pregnant women. Even in labor, when it may be indicated for pain control, meperidine may cause respiratory depression of the mother and her baby, particularly premature babies. Meperidine is excreted in breast milk, and, if needed, should be administered several hours before breastfeeding to minimize ingestion by the infant.

Side effects

The most common adverse effects of meperidine are lightheadedness, dizziness, sedation, nausea and/or vomiting, and sweating. Less common, but more severe, side effects include respiratory depression and abnormally low blood pressure.

Interactions

Individuals who are taking, or who have recently taken, drugs called monoamine oxidase (MAO) inhibitors (a class of antidepressants), should not be given meperidine. Reactions have been reported in this population that are characterized by a variety of signs and symptoms including respiratory distress, coma, abnormally low or abnormally high blood pressure, hyperexcitability, and even death. If administration of a narcotic is required, it should be given in small, gradually increasing test doses under careful supervision.

Adverse effects such as respiratory depression and decreased blood pressure are more common when meperidine is administered in conjunction with other narcotic analgesics, anesthetics, phenothiazines, sedatives, or any other type of drug that suppresses the central nervous system. Alcohol should also be avoided.

Tamara Brown, R.N.

Mercaptopurine

Definition

Mercaptopurine is a medicine used to prevent the formation and spread of cancer cells. Mercaptopurine is

also called 6-mercaptopurine or 6-MP, and is available under the brand name Purinethol.

Purpose

Mercaptopurine is used as part of the consolidation and maintenance treatment for **acute lymphocytic leukemia** (ALL) and **acute myelocytic leukemia** (AML).

Description

Mercaptopurine is an analog of purine, a component of DNA/RNA, and belongs to antimetabolites that prevent the biosynthesis, or utilization, of normal cellular metabolites. It has been used for several decades in combination with other **chemotherapy** drugs for the treatment of different types of acute adult and childhood leukemias (ALL and AML). It has also been shown to be effective for the treatment of inflammatory bowel disease (IBD) (which includes Crohn's disease and ulcerative colitis), certain types of arthritis, and polycythemia vera (above normal increase in red cells in the blood). Mercaptopurine helps to decrease the dose of steroids in patients with IBD, and to reduce their dependence on steroids to control symptoms of their disease. The medicine is taken up by red cells in the blood and works by decreasing the formation of certain genetic material (DNA and RNA) in patients with cancer and by altering the activity of the immune system in patients with IBD.

Recommended dosage

Doses vary between different chemotherapy protocols. The usual dose is 2.5 mg per kg (2.2 pounds) per day in adults and children (50 mg daily in an average 5-year old child or 100–200 mg daily in adults). The total daily dose is calculated to the nearest multiple of 25 mg and is given all at one time. Another way of dosing 6-MP is based on body surface area (BSA), and is usually 75 mg per square meter in children and 80–100 mg per square meter in adults.

Doses of 1.5–2.5 mg per kg per day is recommended for leukemia patients. For those patients with inflammatory bowel disease, doses of 1.5 mg per kg per day have been used in research studies.

Administration

This medicine is usually taken by mouth and should be given at the same time every day, preferably on an empty stomach (one hour before meals or two hours after meals). Children with leukemia should be taking this medicine at bedtime for maximum effectiveness. All patients should drink plenty of fluids (at least eight glasses of water per day) while taking this medication, unless otherwise directed by a physician.

Precautions

The use of 6-MP in pregnant women should be avoided whenever possible, especially during the first three months of pregnancy, as 6-MP can cause birth defects and spontaneous abortions.

As 6-MP can lower the body's ability to fight infections, patients are advised to avoid contact with people who have a cold, flu, or other infections.

Mercaptopurine should be used with caution in the following populations:

- people who had an allergic reaction to 6-MP in the past
- people at risk for pancreatitis (inflammation of the pancreas)
- breastfeeding mothers (it is not known if 6-MP crosses in to breast milk)
- people with liver or kidney disease
- people with gout (6-MP can exacerbate the symptoms of gout)
- people taking **allopurinol** for gout
- people with suppressed bone marrow (tissue filling the empty spaces inside the bone)

Patients are encouraged to stop taking 6-MP, and contact a physician immediately, if any of the following symptoms develop:

- fever, chills, or sore throat
- yellowing of the skin or eyes
- blood in the urine or stools
- black stools
- unusual bleeding or bruising
- stomach pain with nausea, vomiting, or loss of appetite

Patients taking 6-MP must see a physician before starting medication therapy, and also occasionally during therapy, to have blood tests for the monitoring of a complete blood count and kidney and liver functions.

Side effects

This is a very potent medicine that can cause serious side effects. These side effects include skin rash, nausea, vomiting, **diarrhea**, mouth sores, yellowing of the eyes or skin, clay-colored stools, dark urine, decreased ability to fight infections, pinpoint red dots on the skin, and darkening of the skin. Nausea and vomiting, diarrhea, and stomach pain are less common in children than in adults.

KEY TERMS

Consolidation therapy—A stage in treatment of acute lymphocytic leukemia (ALL) that follows induction of remission. The purpose of this stage is to eliminate remaining cancer cells that cannot be detected by usual methods.

Inflammatory bowel disease (IBD)—This disease can be divided into two types: Crohn's disease and ulcerative colitis. Patients with Crohn's disease can have inflammation of the full thickness of the walls of the entire gastrointestinal tract. In patients with ulcerative colitis, the inflammation is limited to the surface of the walls of the large intestine and rectum.

Leukemia—A type of cancer caused by a progressive increase in abnormal blood-forming cells of the bone marrow.

Maintenance therapy—The last stage in treatment of ALL. The purpose of this stage is to provide long-term exposure to lower doses of drugs and to give the immune system time to kill the leukemia cells.

Interactions

Mercaptopurine can decrease the effectiveness of blood thinners such as **warfarin** (Coumadin).

The drug can exacerbate the symptoms of gout. The anti-gout medication, allopurinol, can increase blood levels of 6-MP and increase the risk of its side effects. The dose of 6-MP needs to be decreased, or its use should be avoided, in patients taking allopurinol, which interferes with the degradation of 6-MP.

Risk of liver disease may be increased in patients taking both **doxorubicin** (a cancer chemotherapy drug) and 6-MP. Other medicines that decrease the function of the liver can cause increased toxicity with 6-MP. Patients should inform their doctor or pharmacist about all the prescription drugs and over-the-counter medications that they are taking.

Olga Bessmertny, Pharm.D.

Merkel cell carcinoma

Definition

Merkel cell carcinoma (MCC) is a rare form of cancer that develops on, or just beneath, the skin and in hair follicles. It is also known as neuroendocrine cancer of the skin or trabecular cancer.

Description

Merkel cells are cells that lie in the middle layers of the skin. They are named for their discoverer, a German professor of anatomy named Friedrich Sigmund Merkel (1845–1919). These cells are organized around hair follicles and are believed to act as some type of touch receptors. MCC begins in these cells.

MCC usually appears as firm shiny skin lumps, or tumors. These tumors are painless and can range in size from less than a quarter of an inch (0.6 cm) to over two inches (5.1 cm) in diameter. They may be red, pink, or blue. Tumors first appear on the head and neck in about 48% of cases, and less frequently on other sun-exposed parts of the body.

MCC is very aggressive, it spreads very rapidly, and it often invades other tissues and organs (metastasizes). The most common sites of **metastasis** of MCC are the lymph nodes, liver, bones, lungs, and brain. Metastasis to the lymph nodes generally occurs within seven to eight months after the first skin tumors appear. Nearly half of all people affected with MCC will develop systemic metastases within 24 months, and 67% to 74% of these people will die within five years.

Local recurrence of MCC after the removal of the primary tumor occurs in approximately one-third of all patients and is usually apparent within four months.

Several other names have been used to describe MCC, among these are: anaplastic carcinoma of the skin, apudoma, endocrine carcinoma of the skin, neuroendocrine carcinoma of the skin (NEC), primary small-cell carcinoma of the skin, primary undifferentiated carcinoma of the skin, and trabecular cell carcinoma. The two most commonly used names are MCC and NEC.

Demographics

MCC is seen almost exclusively (94% of known cases)in Caucasians. It affects males more often than females. Seventy-six percent of cases reported in the United States have been diagnosed in people older than 65, but MCC has also been seen in a child as young as seven and a woman as old as 97.

As of 2003, the National Cancer Institute (NCI) had compiled records of 1034 patients in the United States diagnosed with MCC. The number of new cases of MCC is expected to rise as the average life span continues to increase, exposure to the sun remains high, and MCC is recognized more often by medical practitioners.

Causes and symptoms

The cause of MCC has not been positively identified. As of the early 2000s, it is believed to be caused by the skin damage associated with exposure to ultraviolet light from the sun.

Some researchers believe that Merkel cell carcinoma may also be associated with immunodeficiency syndromes, as six of the 1043 patients recorded in the United States developed MCC after being diagnosed with chronic lymphocytic leukemia.

The only symptom of primary MCC is the appearance of the characteristic tumors in the skin. Lymph node metastases show enlarged, firm, lymph nodes in the region of the primary tumor. Other systemic metastases show as masses in the affected organs. The location of the primary tumor is not related to the location of these systemic metastases.

Diagnosis

The diagnosis of MCC is performed by examining and testing a **biopsy** of the tumor. MCC is difficult to differentiate from several other forms of abnormal tissue growth (neoplasms). This diagnosis cannot be made just by examining the tumor cells under a microscope. It is done by performing a variety of chemical tests on these cells. Testing must be performed to make sure this is not metastatic oat-cell (lung) cancer.

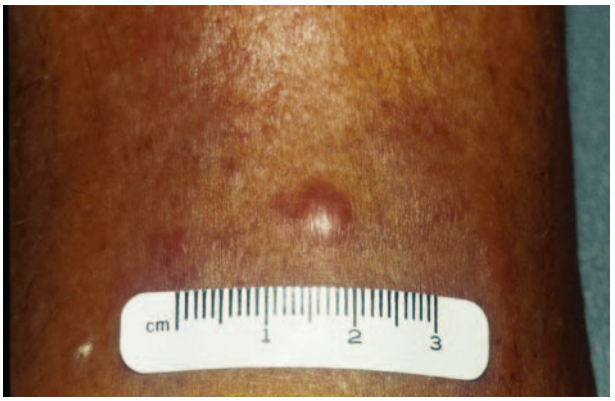
Treatment team

MCC is generally first identified by a microbiologist who examines a biopsy sample. Most MCC tumor removals are performed by dermatologists. Post-operative radiation treatments are generally ordered by the dermatologist and performed by a radiation therapist under the direction of a radiologist and/or a radiation physicist.

Because of the rapid and possibly invasive nature of MCC, patients are generally referred to a physician specializing in cancer (oncologist) to ensure that the disease has not spread to other parts of the body. Chemotherapy for MCC is considered investigational as of late 2003.

Clinical staging, treatments, and prognosis

MCC is classified into three clinical stages. Stage I MCC is defined as a disease that is localized to the skin. Stage II MCC is characterized by a spreading of the disease to the lymph nodes that are near the primary skin tumor or tumors. Stage III MCC is characterized by systemic metastases.



A Merkel cell tumor on a patient's leg. *(Custom Medical Stock Photo. Reproduced by permission.)*

Treatment of stage I MCC involves wide local excision and follow-up **radiation therapy**. Wide local excision is a procedure in which the tumor and a small area of the surrounding healthy tissue are surgically removed. Since MCC is so aggressive, all patients are considered to be at high risk for recurrence and metastasis. For this reason, all patients will undergo radiation therapy of the lymph nodes near the site of the primary tumor that was removed. A technique called lymphoscintigraphy is used to determine the precise location of the lymph nodes that are most likely to be affected.

Treatment of stage II MCC is the same as for stage I MCC with the additional removal of the affected lymph nodes.

Treatment of stage III MCC is generally **chemotherapy**. But, because the number of known cases of MCC is relatively small, there is no generally prescribed chemotherapy regimen. It has been treated with **etoposide**, cisplatin, and **fluorouracil** with varying degrees of success.

The prognosis for patients affected with MCC is generally poor. Half will have a recurrence within two years and one-third will develop systemic involvement (stage III). The average time span from diagnosis of stage III MCC to death is eight months. The two-year survival rate for people affected with MCC is approximately 50%. Factors that improve the patient's length of survival include location of the tumor on the limbs rather than the face; localization of the disease; and female sex.

Alternative and complementary therapies

Naturopathic remedies believed by some to be beneficial in the prevention of skin cancers include regular cleansing by fasting, enema, or herbal supplements. Many naturopaths also recommend a daily scrubbing of the skin with a sauna brush prior to bathing to increase circulation.

KEY TERMS

Merkel cells—Specialized cells of the skin that are located at the base of some hairs. These cells are believed to function as touch receptors. They are named for a nineteenth-century German professor of anatomy.

Metastasis—The migration of a cancer from its primary location to another, distant location in the body.

Neoplasm—Any new and abnormal growth of a tissue.

QUESTIONS TO ASK THE DOCTOR

- What stage is my cancer in?
- How long will my radiation therapy treatments last after the tumor is removed?
- What are the possible side effects of the particular radiation or chemotherapy treatments that I will receive?
- How often should I continue to be checked for possible recurrence of MCC?

Vitamins A, C, and E, as well as zinc, are believed by some to be essential supplements to a high fiber diet in the prevention of skin damage. However, these remedies have not been proven effective in treating Merkel cell tumors. Traditional medical treatments which have succeeded include surgery, radiation therapy, chemotherapy, and rare success with stem cell transplant.

Coping with cancer treatment

The radiation therapy necessary for follow-up treatment after MCC tumor removal can become stressful for some patients. Additionally, most of these cancers occur in the head and neck region, and their removal can be very disfiguring. It is important that all patients receive adequate counseling and other psychological support prior to and during such treatments.

Clinical trials

In late 2003, the National Cancer Institute was conducting three phase II studies of treatments for Merkel cell carcinoma: a study of antineoplaston therapy for MCC; a study of imatinib mesylate, a drug that blocks enzymes necessary for tumor growth; and a study of oblimersen, a drug that blocks the production of a crucial protein in cancer cells.

Prevention

Because MCC is believed, at least in some cases, to be caused by long-term exposure to ultraviolet light, it may possibly prevented by avoiding sun exposure when possible and by wearing a PABA containing sunscreen daily.

Special concerns

MCC is very aggressive and can metastasize quickly. For these reasons, medical treatment needs to be sought quickly when MCC is suspected. Recurrence of MCC, either on the skin or in the lymph nodes or other bodily organs, is quite common. Therefore, it is extremely important that all MCC patients, even if they believe that they have no symptoms, have follow-up examinations monthly for at least two years after they have finished their initial radiation treatments.

Resources

PERIODICALS

Agelli, M., and L. X. Clegg. "Epidemiology of Primary Merkel Cell Carcinoma in the United States." *Journal of the American Academy of Dermatology* 49 (November 2003): 832–841.

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ORGANIZATIONS

American Academy of Dermatology (AAD). P. O. Box 4014, Schaumburg, IL 60168-4014. (847) 330-0230. Fax: (847) 330-0050. <http://www.aad.org>.

American Cancer Society. (800) ACS-2345. <http://www.cancer.org>.

The Skin Cancer Foundation. 245 Fifth Ave., Suite #1403, New York, NY 10016. (800) SKIN-490. <http://www.skincancer.org>.

OTHER

CancerNet: Merkel Cell Cancer. [cited June 27, 2005]. <http://www.cancer.med.upenn.edu/pdq/600611.html>.

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Paul A. Johnson, Ed.M.
Rebecca J. Frey, Ph.D.

Mesna

Definition

Mesna is a medicine that helps protect the inside lining of the bladder from damage due to certain **chemotherapy** drugs. Mesna may also be referred to as 2-mercaptoethane sulfonate, sodium salt, or Mesnex (its brand name).

Purpose

Mesna is a medicine that is approved by the Food and Drug Administration (FDA) for use in combination with the chemotherapy drug **ifosfamide** to protect the bladder lining from irritation due to the chemotherapy. It has also been shown useful in protecting the bladder lining when used in combination with large doses of the chemotherapy drug **cyclophosphamide**. Irritation to the bladder lining can cause bleeding and this is referred to as hemorrhagic cystitis. Mesna is not administered to treat cancer.

Description

Mesna is a clear, colorless solution with a foul odor. It is usually administered intravenously through a vein to prevent bleeding of the inside lining of the bladder. Sometimes it can be given to a patient to mix in a beverage and drink. When ifosfamide and cyclophosphamide are given, they break down in the body and form a poisonous substance called acrolein. Acrolein concentrates in the bladder and causes irritation that can lead to severe bleeding from the bladder into the urine. When mesna is administered it also concentrates in the bladder and combines with the toxic acrolein to form a nontoxic substance that is removed from the body by urinating.

Recommended dosage

Mesna is usually administered through a vein over at least five minutes. This same drug can also be mixed with a beverage and taken by mouth (flavored drinks like grape juice, cola, and chocolate milk are good choices to hide the taste of the mesna).

The mesna dose depends on the amount of chemotherapy drugs, ifosfamide or cyclophosphamide, that a patient receives. The mesna dose can vary with the time frame the chemotherapy drugs are being administered. The standard mesna dose is equal to 20% of the total ifosfamide dose given at three separate time intervals through a vein infused over at least five minutes. The first dose is right before the ifosfamide, often referred to as hour 0. The second dose is four hours after the start of the infusion and the third dose is eight hours after the start of the infusion. Mesna is given in this way each day the ifosfamide is administered.

Mesna can be given at a dose of 100% (the same dose as the ifosfamide) of the ifosfamide. This mesna would be mixed directly with the ifosfamide in the same intravenous infusion bag. This type of dosing may or may not have the patient receive a small dose of mesna right before or after the ifosfamide infusion.

Precautions

Mesna can cause allergic reactions that range from a mild rash to severe life-threatening, full-body allergic reactions. Patients with a known previous allergic reaction to mesna or thiol-like medicines should tell their doctor before receiving mesna.

Mesna that contains the preservative benzyl alcohol must not be used in premature babies or infants and must be used with caution in older children.

Mesna should prevent most bleeding from the bladder, however patients may be asked to check their urine for traces of blood with a chemical strip that is dipped into the urine sample.

Side effects

Side effects due only to the mesna are uncommon and difficult to determine since the drug is not given alone. However in clinical studies mesna has been known to cause nausea and vomiting, **diarrhea**, abdominal pain, and a bad taste in the mouth. Other reported side effects include; headache, fatigue, pain in arms and legs, drop in blood pressure, and allergic reactions.

All side effects a patient experiences should be reported to his or her doctor.

KEY TERMS

Acrolein—A breakdown product of the chemotherapy drugs ifosfamide and cyclophosphamide that concentrates in the bladder and irritates the bladder lining and causes bleeding.

Bladder—Organ in the body that collects urine from the kidneys.

Chemotherapy—Specific drugs used to treat cancer.

Food and Drug Administration—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives the approval to pharmaceutical companies for commercial marketing of their products.

Hemorrhagic cystitis—Irritation of the bladder lining that causes bleeding.

Nontoxic—Does not cause harm.

Interactions

Mesna can cause a false positive test of the urine for ketone bodies. This may be most important in diabetic patients who routinely check their urine for ketones.

Nancy J. Beaulieu, RPh.,BCOP

Mesothelioma

Definition

Mesothelioma is a rare form of cancer. In mesothelioma, malignant cells are found in the sac lining of the chest (the pleura) or the abdomen (the peritoneum). The majority of people with mesothelioma have a history of jobs that exposed them to asbestos, an insulation material.

Description

In the chest and abdominal cavities, as well as in the cavity around the heart (pericardial sac), there is a layer of specialized cells called mesothelial cells. These cells also surround the outer surface of most internal organs. These cells form tissue called mesothelium.

The mesothelium performs a protective function for the internal organs by producing a lubricating fluid that permits the organs to move around. For example, this fluid makes it easier for the lungs to move inside the chest while a person breathes. The mesothelium of the abdomen is known as the peritoneum, and the mesothelium of the chest is called the pleura. The pericardium refers to the mesothelium of the pericardial cavity.

There are three primary types of malignant mesotheliomas:

- Epithelioid. About 50% to 70% of mesotheliomas are of this type and have the best outlook for survival.
- Sarcomatoid. Approximately 7% to 20% of cases are of this type.
- Mixed/biphasic. From 20% to 35% of mesothelioma cases fall into this category.

Approximately three-fourths of all mesotheliomas begin in the chest cavity and are known as pleural mesotheliomas. Peritoneal mesotheliomas begin in the abdomen, and make up around 10% to 20% of all cases. Mesotheliomas arising in the cavity around the heart are quite rare.

Demographics

Mesothelioma is a fairly rare form of cancer. According to the American Cancer Society, there are an estimated 2,000 to 3,000 new cases per year of the disease in the United States, but this figure seems to be rising. This rising figure is related to the widespread use of asbestos from the 1940s to the end of the 1970s. European researchers studying the disease expect deaths from mesothelioma to peak around the year 2020 and then drop off, because asbestos use has been cut back greatly since the early 1980s.

The average age of a person with mesothelioma is 50 to 70 years old. It affects men three to five times more often than women and is less common in African-Americans than in Caucasian Americans.

Causes and symptoms

The primary risk factor for developing mesothelioma is asbestos exposure. In the past, asbestos was used as a very effective type of insulation. The use of this material, however, has been declining since the link between asbestos and mesothelioma has become known. It is thought that when the fibers of asbestos are inhaled, some of them reach the ends of the small airways and penetrate into the pleural lining. There the fibers may directly harm mesothelial cells and eventually cause mesothelioma. If the fibers are swallowed, they can reach the abdominal cavity, where they can contribute to the formation of peritoneal mesothelioma.

Exposure to certain types of radiation as well as to a chemical related to asbestos known as zeolite has also been related to incidences of mesothelioma.

The early symptoms of mesothelioma are often ignored, because they may be caused by a variety of ailments. These symptoms include:

- pain in the lower back or at the side of the chest
- shortness of breath
- difficulty swallowing
- cough
- fever
- fatigue
- abdominal pain, **weight loss**, and **nausea and vomiting** (symptoms of peritoneal mesothelioma)

Diagnosis

A doctor should be seen if a person experiences shortness of breath, chest pain, or pain or swelling in the abdomen. If these symptoms are present, the doctor may order an **x ray** of the abdomen or chest. The doctor will do a complete physical examination and take a thorough medical history. Then, one or more of the following methods may be used to ascertain whether mesothelioma is present.

- Imaging tests. These tests may include x rays, **computed tomography** (CT scans), or **magnetic resonance imaging** (MRI) to allow the doctor to visualize the area in question. These studies will help determine the location, size, and extent of the cancer.
- **Pleural biopsy**. Diagnosing mesothelioma requires an adequate **biopsy** specimen. However, because mesothelioma usually arises from the lower part of the diaphragmatic and/or parietal pleura, obtaining enough tissue may be difficult. A simple, or closed, pleural biopsy involves the insertion of a needle into the chest cavity to obtain tissue from the pleural membrane for analysis. This technique is minimally invasive and normally requires only local anesthesia. This technique, however, may not provide adequate material for the necessary stains of the tissue to make a diagnosis of mesothelioma. Moreover, since the biopsy is not done under direct vision, the sample may not be exactly in the area of the tumor. If the diagnosis cannot be made with this relatively noninvasive technique, an adequate tissue sample usually can be obtained via an open pleural biopsy. In this approach, a surgeon makes an incision on the patient's side and goes into the pleural space. This method allows maximum exploration of the pleural membranes as well. However, the technique requires general anesthesia.
- **Thoracoscopy**. A thoracoscopy, which is a relatively new technique, allows the doctor to look directly into the chest (pleural) cavity at the tumor and during the same operation to also take a tissue sample for laboratory analysis. The thoracoscopy is performed by making a small incision into the chest and using a tiny video camera to inspect the region. The doctor can then use forceps to obtain a tissue biopsy. A **laparoscopy**, a similar operation, is used to obtain a biopsy of a peritoneal tumor.
- **Bronchoscopy**. A bronchoscopy, which examines the airways, or a **mediastinoscopy**, which looks at the lymph nodes in the chest, allows the doctor to look at the area using a lighted tube. Samples may be taken with a needle and sent to the lab to find out if cancer cells are present. However, bronchoscopy and mediastinoscopy are not that effective for diagnosing mesothelioma, as the disease is seldom found within the airways or the lymph nodes.
- Surgery. This lets the doctor obtain a larger tumor sample or, on occasion, the entire tumor.

Diagnosing mesothelioma is often difficult, even with tissue biopsies. Microscopically, mesothelioma is often difficult to distinguish from several other forms of cancer. For this reason, certain laboratory tests are performed to help correctly diagnose mesothelioma. Some of these tests involve using antibodies to distinguish lung cancer from mesothelioma. Sometimes the tissue samples must be viewed under an electron microscope in order to get the correct diagnosis.

Treatment team

A person with symptoms of mesothelioma will most likely seek help from a primary physician initially. During the diagnostic phase, various technicians will perform the **imaging studies**. A specially trained physician—a thoracic surgeon or, rarely, a pulmonologist—performs other diagnostic tests like pleural biopsy and thoracoscopy. A pathologist will view the tissue samples and make the tissue diagnosis. Following diagnosis, the patient will be offered some form of treatment, which may entail surgery, **radiation therapy**, **chemotherapy**, or a combination of these. The patient may receive care from a thoracic surgeon, an anesthesiologist, medical and radiation oncologists, and specially trained nurses who administer chemotherapy.

Clinical staging, treatments, and prognosis

The treatment and outlook for those with mesothelioma depends a great deal on the stage of their cancer. Because the most frequently occurring type of mesothelioma is pleural, and it is also the one most studied, it is

the only type for which a staging system exists. The following stages are based on a system known as the Butchart system, which divides mesothelioma into four stages:

- Stage I: Mesothelioma is found within the right or the left pleura and may also involve the lung, the pericardium, or the diaphragm on the same side.
- Stage II: In this stage, mesothelioma has spread to the chest wall or involves the esophagus, the heart, or the pleura on both sides. The lymph nodes in the chest may be involved as well.
- Stage III: Mesothelioma has gone through the diaphragm and into the lining of the abdominal cavity. Additional lymph nodes besides those in the chest may be involved.
- Stage IV: There is evidence that mesothelioma has spread through the bloodstream to distant organs or tissues.

Another system of staging mesothelioma is based on a TNM system (T=tumor, N=spread to lymph nodes, and M=metastasis). There are minor differences between this and the Butchart system. It is more detailed and precise, but the original Butchart system is still the one most often used to describe pleural mesotheliomas.

There are treatments available for all patients with malignant mesothelioma. The three kinds of treatment used are surgery, radiation therapy, and chemotherapy.

Surgery is a common treatment for mesothelioma. It is not an option unless the cancer is limited to one place and unless the person can withstand the surgery. During surgery, the physician may remove a portion of the lining of the chest (pleurectomy) or abdomen (peritonectomy) and some of the tissue surrounding it. Depending on the extent the disease has spread, a lung may also require removal (extrapleural **pneumonectomy**). Occasionally, a portion of the diaphragm is taken out as well. If treatment is not possible, other less invasive measures can be used to relieve the patient's symptoms. For example, a needle placed into the chest cavity (**thoracentesis**) can remove excess fluid in the chest. If recurrence of fluid causes symptoms, a nonsurgical or surgical method can be used to scar the lining of lung cavity and cause it to adhere to the lung. The procedure obliterates the pleural space and thus prevents the fluid from reaccumulating. (This procedure is called sclerosis or sclerotherapy.) These methods are called palliative, for they are not meant to cure the cancer but to improve symptoms.

Radiation therapy uses high-energy x rays to kill cancer cells and cause tumor shrinkage. It is rarely used as the primary treatment for pleural mesothelioma in those patients for whom surgery is not an option. It may also be used as an adjunct to surgery or as a method of alleviating various symptoms like trouble with swallowing, pain, and shortness of breath.

Chemotherapy involves the use of drugs to kill cancer cells. The most commonly used drugs are **doxorubicin**, **cisplatin**, and **methotrexate**. The medicines are delivered into a vein or taken by mouth. In the treatment of mesothelioma, they may also be injected directly into the chest or abdominal cavity. Chemotherapy may be given as the main treatment or may be an addition to surgery, depending on the type and stage of the cancer.

A new treatment being studied for early stages of mesothelioma confined to the chest is called intraoperative photodynamic therapy. This treatment uses special drugs that make cancer cells more sensitive to killing by a laser light. The drugs are given several days before surgery. During surgery, the special light is used to shine on the pleura.

By the time symptoms show up and mesothelioma is diagnosed, the disease is often advanced. The average survival period after diagnosis is about one year. If the cancer is found before it has spread and it is treated aggressively, about half of the patients will live two years, and approximately 20% will survive five years.

Alternative and complementary therapies

There are no proven effective alternative therapies for mesothelioma. Because the prognosis is often poor, many patients may be interested in trying other avenues of treat-

KEY TERMS

Asbestos—A group of naturally occurring fibrous minerals, found in soil and rocks around the world. These minerals are composed of magnesium, silicon, and other elements. Asbestos has been used as an insulating material since ancient times. Exposure to asbestos dust is the primary risk factor for developing mesothelioma.

ment. Patients should first consult with their physicians prior to trying any of these methods. There are many well-studied complementary treatments that may increase a patient's comfort and sense of well-being. These may include meditation to aid in relaxation, massage to decrease pain, and guided imagery to help prevent nausea.

Coping with cancer treatment

Coping with cancer treatment can be difficult and exhausting. It can be very helpful for the patient receiving therapy for mesothelioma to find a group of family and friends who can aid with household responsibilities, provide transportation, and give psychological support. The patient should not feel a need to rush back to normal activities after treatment is completed.

Clinical trials

A great deal of research is being performed in the area of mesothelioma. Much of the research is focused on finding out how asbestos changes the mesothelial cells to cause these cancers. In addition, new combinations of treatments are being tested, along with gene therapy. A variety of **clinical trials** are testing new chemotherapy drugs and immunotherapy. Some of these treatments use hormonelike substances called interleukins and **interferons** that activate the immune system.

Prevention

The best method of preventing mesothelioma is to avoid or limit exposure to asbestos. People who might experience asbestos exposure at work include miners, insulation manufacturers, construction workers, ship builders, and factory workers.

Special concerns

Mesothelioma is a serious disease with a poor long-term prognosis. Patients with this cancer should communicate their wishes regarding treatment to their family and physicians.

QUESTIONS TO ASK THE DOCTOR

- What type of mesothelioma do I have?
- Has my cancer spread beyond the primary site?
- What stage is my cancer in? What treatment options are there?
- What is my prognosis?
- Are there experimental therapies I may benefit from? Where are they being performed?

Resources

PERIODICALS

Apgar, Barbara. "Diagnosis of Malignant Pleural Mesothelioma." *American Family Physician* January 15, 2000: 536.

ORGANIZATIONS

American Cancer Society. (800) ACS-2345. <http://www.cancer.org>.

National Cancer Institute. Building 31, Room 10A31, 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. <http://www.nci.nih.gov>.

Deanna Swartout-Corbeil, R.N.

Metastasis

Definition

The ability to invade and metastasize are the defining characteristics of a cancer. Invasion refers to the ability of cancer cells to penetrate through the membranes that separate them from healthy tissues and blood vessels. Metastasis can refer either to the spread of cancer cells to other parts of the body, or to the condition produced by this spread. The English word metastasis (plural, metastases) comes from a Greek word that means "a change." The tumors produced by metastasis sometimes are called secondary tumors. metastasis is responsible for 90% of the deaths caused by cancer.

Description

Metastasis is a complex multi-step process that begins with changes in the genetic material of a cell (**carcinogenesis**) followed by the uncontrolled multiplication of altered cells. It continues with the development of

a new blood supply for the tumor (angiogenesis), invasion of the circulatory system, dispersal of small clumps of tumor cells to other organs or parts of the body, and the growth of secondary tumors in those sites.

Carcinogenesis and genetic mutations

The first step in cancer development is a change or mutation of the DNA in the chromosomes of a cell. Mutations can be triggered by a number of different factors, including:

- Environmental carcinogens. Ultraviolet radiation from the sun is known to cause skin cancer. Chemical carcinogens include tobacco smoke, asbestos, and benzene. Ionizing radiation from x-ray therapy or atomic fallout, or industrial exposure to uranium or thorium are also associated with an increased risk of cancer.
- Viruses. Infection by a virus containing an oncogene is known to cause cancer in experimental animals. In humans, such viruses as human immunodeficiency virus (HIV), human papillomavirus (HPV), hepatitis B or C viruses, and **Epstein-Barr virus** (EBV) have been linked to **Kaposi's sarcoma**, **anal cancer**, certain types of **lymphoma**, primary liver cancer, and cancers of the genitals.
- Chronic irritation and inflammation. Chronic irritation of the skin, or chronic inflammation of the bladder or bile ducts caused by certain intestinal parasites, have been linked to cancers of the skin, bladder, or pancreas.
- Chromosomal rearrangement or damage. Oncogenes are genes found in the chromosomes of tumor cells. Activation of oncogenes is associated with the conversion of normal cells into cancer cells. Oncogenes sometimes are activated by chromosomal rearrangements. The so-called Philadelphia chromosome, an abnormality that involves a transposition of genetic material between the long arms of human chromosomes 9 and 22, is found in about 80% of patients with chronic myelocytic leukemia.
- Loss of tumor suppressor genes. Another type of genetic alteration that can lead to cancer is the inactivation of anti-oncogenes, or tumor suppressor genes. Under normal circumstances, tumor suppressor genes act like a brake on cell growth and division. If these genes are altered or lost, oncogenes can stimulate cells to multiply uncontrollably without any opposition. In colorectal cancer, deletion of the DCC gene, which is a tumor suppressor gene located on the long arm of human chromosome 18, lowers the patient's chances of five-year survival by 30%.

Other mutations in a cell's DNA occur for reasons that are not yet fully understood.

Steps in the development of metastases

Cell alteration and replication

Most cancer cells originate within the epithelium, which is a layer of tissue that covers body surfaces and lines the inner surfaces of body cavities and blood vessels. Cancer cells in epithelial tissue are known to be genetically unstable and to have a high mutation rate. Most cancers, in fact, are the end result of multiple genetic alterations both in oncogenes and tumor suppressor genes. The activation of oncogenes is accompanied by the loss or deactivation of tumor suppressor genes, which means that one of the body's normal lines of defense against uncontrolled cell proliferation is disabled just when it is most needed.

Following these alterations in its genetic material, the cell replicates, or copies itself at a faster rate. In some instances, a mutation prevents the cell's apoptosis, or programmed self-destruction. Apoptosis, which is also sometimes called "cell suicide," normally occurs when a cell recognizes some damage to its DNA and dies. The protein produced by the p53 gene ordinarily encourages apoptosis in cells with defective DNA, but these cells are more likely to survive and replicate if the p53 gene has been altered or deactivated.

Breaking through the basement membrane

Once a cancer develops, the first stage in the development of metastasis is the tumor's penetration of the basement membrane, which separates epithelial tissue from underlying connective tissue. The basement membrane is a specialized layer of extracellular matrix, which is a mass of connective tissue fibers and proteins that support and nourish the body's connective tissues. Under normal circumstances, the extracellular matrix is a barrier that keeps cells from moving away from their sites of origin. Cancer cells, however, secrete several different types of enzymes that digest the proteins in the basement membrane. When the membrane has been sufficiently weakened, the tumor can push through it.

Angiogenesis

Angiogenesis is the process in which a tumor creates its own blood supply by releasing growth factors—particularly a substance called vascular endothelial growth factor, or VEGF—that attract vascular cells that begin to migrate toward the tumor. The vascular cells eventually form new blood vessels within the tumor. Angiogenesis is sometimes called vascularization, which means blood vessel formation. Angiogenesis is a significant step in the development of metastasis for two reasons: the formation of blood vessels in

the tumor supplies the tumor with nutrients that speed up its growth; these vessels also provide pathways for cancer cells to travel from the primary tumor to other organs. A similar process of vessel formation involves the lymph system.

Angiogenesis may occur at about the same time that the tumor breaks through the basement membrane, but it can also take place at an earlier point in the tumor's growth.

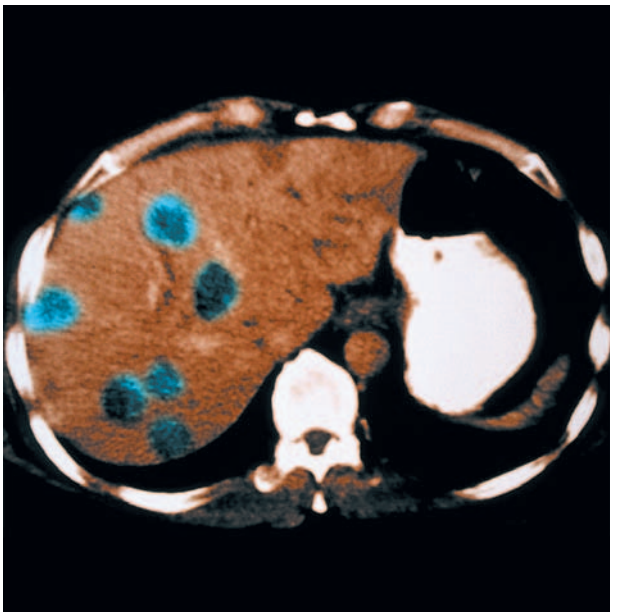
Invasion and embolization

After the tumor's new blood vessels have formed, individual cancer cells break off from the tumor and travel through these new vessels into the body's main circulatory system. These cells are sometimes called micrometastases. Even a small tumor can shed as many as a million cancer cells each day into the blood and lymph vessels. Most of these cells die soon after entering the blood stream or lymph vessels. Sometimes, however, the cancer cells may travel as small clumps of cells called emboli. A protein called fibrin, which ordinarily is formed when blood clots, surrounds each embolus. The fibrin appears to protect the embolus of cancer cells as it moves through the circulatory system, and may increase its chances for survival when it arrives in the capillaries (small blood vessels) that supply another organ or area of the body.

Extravasation and formation of secondary tumors

Extravasation refers to the cancer cell's breaking out through the wall of the capillary where it has been stopped and invading the tissue around the capillary. In order to extravasate, the tumor cell must attach itself to the wall of the capillary. Once it has attached itself, it can work its way through the tissue lining the blood vessel, the vessel wall itself, and the basement membrane covering the blood vessel. The tumor cell can then begin to replicate itself and start the process of angiogenesis, thus forming a metastasis or secondary tumor in its new location. The secondary tumor can eventually release its own cancer cells into the circulation and produce further metastases.

Most tumor cells do not survive in the blood stream long enough to extravasate and form metastases. The longer the cells are in the circulation, the more likely they are to die. The chances of a given tumor cell's surviving the journey and forming a metastasis in its new site have been variously estimated as one in 10,000 or as less than one in one million. Researchers have asked whether the tumor cells that do produce metastases are random survivors or whether they have special capacities for survival and reproduction. Recent studies indicate that cells from the same tumor vary in their metastatic potential; those that eventually form metastases have a higher degree of malignancy.



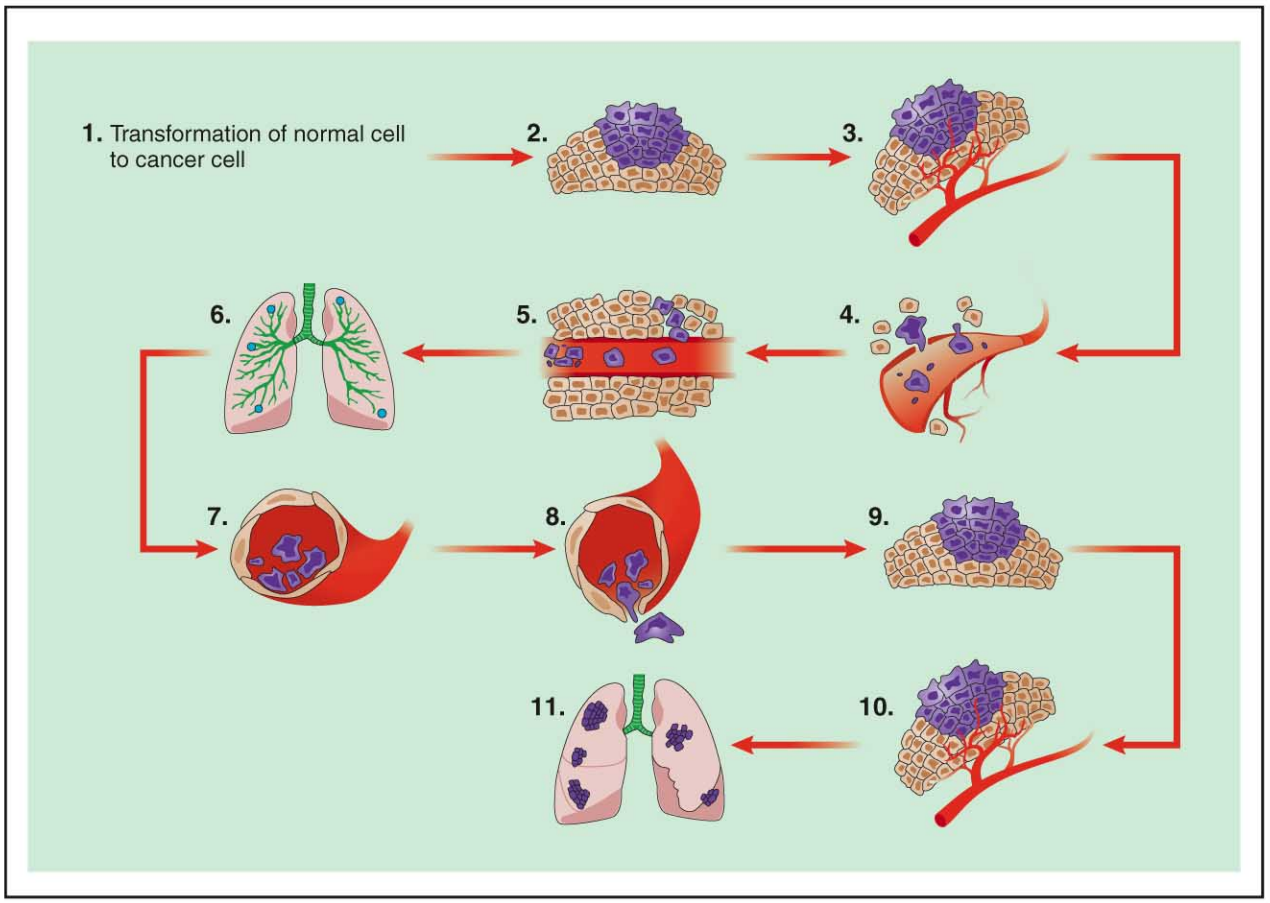
Computed tomography (CT) scan of abdomen revealing liver metastases from colon adenocarcinoma. *(Copyright Scott Camazine & Sue Trainor, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Diagnosis and monitoring of metastases

Some primary cancers, such as lung and ovarian cancers, begin to shed tumor cells that form metastases elsewhere in the body before the primary cancer is large enough to be detected by standard diagnostic techniques. Marker molecules that are given off by micrometastases circulating in the bloodstream can now be detected.

Tumor markers are substances produced either by tumors themselves or by the body in response to a tumor. The blood levels of tumor markers can be used to evaluate the recurrence or spread of cancer and the patient's response to treatment. Some commonly used tumor markers include: prostate-specific antigen (PSA) for **prostate cancer**; prostatic acid phosphatase (PAP) for prostate cancer that has metastasized, **testicular cancer** and leukemia; and CA 125 (Cancer antigen 125) for recurrence of **ovarian cancer**. It also detects cancers of the uterus, liver, pancreas, colon, cervix, lung, and digestive tract, as well as several others.

DNA analysis can be used to distinguish metastatic tumors from multicentric tumors. A multicentric cancer is one that appears simultaneously in several different



(1) A cell is transformed. (2) Cancerous cell proliferates and cells pile up to form a malignant tumor. (3) Angiogenesis: the tumor acquires a blood supply, which also allows (4) the cancer cells access into the circulatory system. (5) Cancer cells travel through the blood stream. (6) The cells stop in a capillary bed, and (7) adhere to the layer of cells that line the blood vessel. (8) The cells invade the essential, functional tissue of the organ surrounding the blood vessel. (9) In this new organ, cancer cells pile up to form secondary tumors, which (10) induce angiogenesis. (11) Metastases (secondary tumors) are now evident. *(Illustration by Argosy Publishing.)*

parts of the body, as distinct from cancers with primary and secondary (metastatic) tumors. Mutations in the p53 tumor suppressor gene have been used as "genetic fingerprints" to identify differences between multicentric and metastatic tumors.

Specific types of metastases

Brain

SYMPTOMS Metastatic tumors to the brain usually come to the doctor's attention in the same way as primary tumors—they cause increased pressure inside the head, disturbances of brain functions, or both. Common symptoms of brain metastases include headaches, seizures, loss of sensation or balance, or personality changes.

SOURCES The most common source of brain metastases is primary cancer of the lung. Other primary sources include malignant melanomas and cancers of the breast, kidney, or digestive tract.

DIAGNOSIS Secondary brain tumors are usually detected on (**computed tomography**) (CT) scans or (**magnetic resonance imaging**) (MRI) studies.

TREATMENT If the patient has only one secondary tumor in the brain, it is sometimes possible to remove it surgically and then treat with radiation. Otherwise, radiation is used by itself to treat the tumors. Steroids may be given to reduce or lower swelling of the brain, treating the headaches and other symptoms. **Chemotherapy** has only a limited role in treating brain metastases, because most chemotherapy drugs cannot cross the blood-brain barrier. However, intrathecal chemotherapy (chemotherapy drugs injected directly into the spinal fluid) can have a role in treating brain metastases. Patients with multiple metastases in the brain or widespread cancer elsewhere in the body have a poor prognosis. Treatments that are

still under evaluation include laser-assisted surgery and biological response modifiers.

Bone

SYMPTOMS Primary bone cancers are less common than bone metastases. Bone metastases, in fact, are a common cause of pain in many patients with late-stage cancer. Metastases in the spine can compress the spinal cord and damage the nervous system. Bone metastases also make bones more prone to fracture.

SOURCES Breast, lung, and prostate cancer are responsible for about 80% of bone metastases; over half of patients with these three types of primary cancer will develop bone metastases. Patients with lung cancer that has metastasized to bone live on average less than six months, but breast and prostate cancer patients may have lengthy periods of survival with bone metastases.

Bone metastases usually are caused by tumor cells carried through the bloodstream, and are typically multiple. About 70% of bone metastases occur in the ribs, spine, sacrum (lowest portion of spine, attached to pelvis), or head; most of the remainder occur in the long bones of the body.

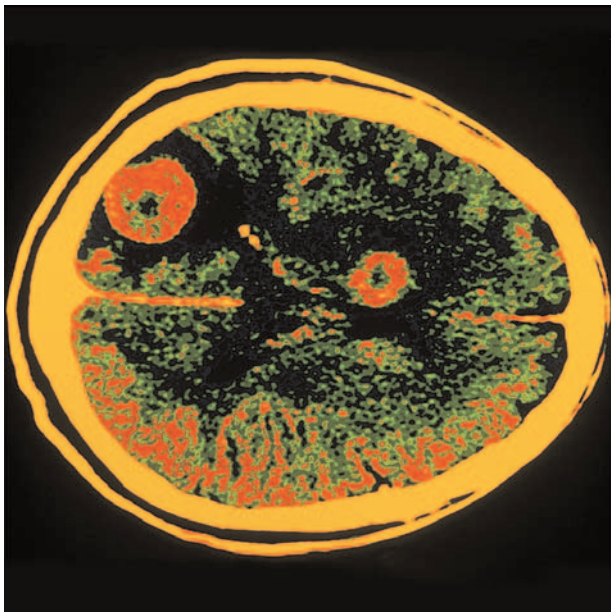
DIAGNOSIS Bone metastases usually are detected by bone scans, CT scans, or MRIs, and confirmed by a **biopsy**. In 2003, reports showed that positron emission tomography (PET) scans were effective in detecting certain types of bone mestasteses from lung and breast cancer and from lymphoma.

TREATMENT Bone metastases are treated with hormonal or systemic chemotherapy and/or **radiation therapy**. Metastases in the spine may require surgical removal of part of the vertebrae (laminectomy) followed by radiation treatment to prevent compression of the spinal cord. Surgery also may be performed if there is a risk of fracture.

As of May 2001, two new drugs show promise as treatments for bone metastases. One is a generic drug called clodronate, which is taken by mouth, and the other is a medication called Atrasentan. Atrasentan was tested on patients in advanced stages of bone metastases who were no longer responding to other forms of treatment.

Lung

SOURCES Metastatic tumors in the lungs may result either from primary cancer of the lung or from malignancies elsewhere in the body that spread to the lungs through the circulatory system or by direct extension. The incidence of metastatic cancer to the lung is six in 100,000 people. Almost any type of cancer can metastasize to the lung, but the most common tumors that spread to the lung are **breast cancer**, **sarcomas**, non-Hodgkin's lymphoma, **neuroblastoma**, and **Wilms' tumor**. Between 20% and 54% of patients dying of cancer are found to have metastases in the lungs.



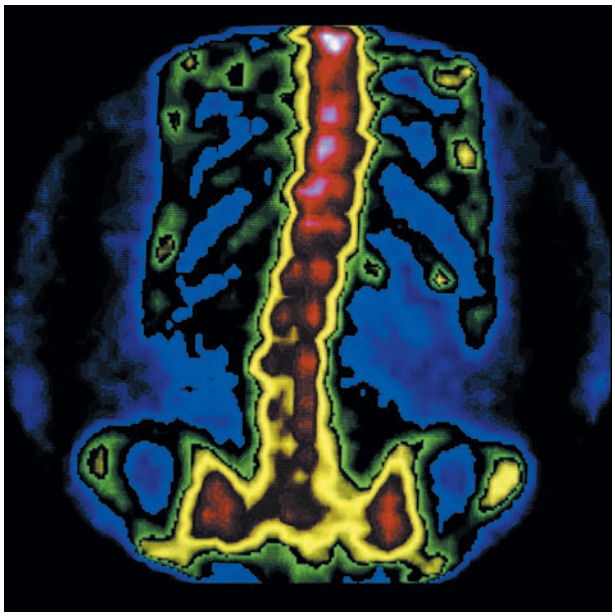
Computed tomography (CT) scan of 47-year-old female's brain showing adenocarcinoma of lung metastatic to brain. *(Copyright Scott/Brian Carmazine, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

DIAGNOSIS Diagnosis is usually the appearance of a group of masses on a chest **x ray**. Evaluation of lung metastases is first directed at diagnosing/locating the primary tumor.

TREATMENT Secondary lung cancers are treated primarily by appropriate systemic therapy for the primary tumor. Surgery for secondary lung tumors may be beneficial if there are four or less metastases. Surgical removal of tumors metastatic to the lung is usually performed only if: the primary tumor is treatable, all metastases can be removed, chemotherapy or other nonsurgical approaches cannot be used, and if there are no metastases elsewhere in the patient's body. If the primary cancer is a malignant **melanoma** and there is only one secondary tumor, surgery may be an option. (Surgery is usually not performed if the primary cancer is a malignant melanoma and there is more than one secondary tumor.) The five-year survival rate for surgical treatment of secondary tumors to the lung is 20%-35%.

Liver

The most common form of liver cancer is metastatic; in fact, metastases in the liver are often the first



False-color scintigram (bone scan) of the human spine and ribs, revealing secondary cancers (metastases) in the vertebrae (backbones), arising from a primary cancer of the prostate gland. *(Copyright CNRI, Science Source/ Photo Researchers, Inc. Reproduced by permission.)*

noticeable evidence of a primary cancer located elsewhere in the body. In the liver, finding multiple metastases is more common than finding a single tumor. The liver's important role within the circulatory system makes it a common stopping point for tumor emboli carried in the blood from other organs.

SOURCES The most common sites of primary tumors that metastasize to the liver are the lungs, breasts, colon, pancreas, and stomach.

DIAGNOSIS The diagnosis of metastatic liver cancer is usually difficult unless the patient's primary tumor is in advanced stages of disease. Ultrasound, CT scans, and liver function tests are used to screen patients with a known cancer for metastases in the liver, but the results are not fully reliable. A definitive diagnosis depends on biopsy of liver tissue.

TREATMENT Metastatic cancer to the liver is considered incurable. Systemic chemotherapy may temporarily shrink tumors in the liver and extend the patient's life span but does not cure the cancer. Radiation treatment may relieve pain but is not otherwise helpful. Some doctors may recommend surgical removal of liver metastases, particularly if the primary tumor is in the colon and there is a solitary metastasis, but others do not favor this approach. The five-year survival rate for surgical removal of liver metastases is 20%-30%.

Metastatic cancers of unknown primary origin

Between 0.5% and 7% of all cancers are carcinomas of unknown primary origin, or CUPs. The patient's history and physical examination should be analyzed for signs of breast, prostate, pelvic, rectal, and **gastrointestinal cancers**. The pattern of spread of a CUP may indicate whether the primary tumor is above or below the diaphragm; lung metastases are twice as common with primary tumors found to be above the diaphragm, while liver metastases are more common if the **primary site** is below the diaphragm.

Metastases of unknown primary origin are usually treated by chemotherapy—either cisplatin/carboplatin, **doxorubicin** or **paclitaxel**. In most cases, the patient's prognosis is poor; the average length of survival is three to four months, with fewer than 10% of patients surviving five years. Male sex and involvement of the liver are negative factors in the prognosis.

Treatment

Surgery

Surgery as a method of cancer treatment has limitations in the therapy of metastatic cancer. It is sometimes used to remove large secondary tumors that are causing pain or interfering with body functions. It also may offer a survival advantage over other therapies, as with limited metastases to the lung or liver.

Chemotherapy

Chemotherapy is frequently used to treat micrometastases that have entered the patient's bloodstream or lymphatic system. Systemic chemotherapy is the only type of treatment that can act at multiple sites simultaneously. Because of some chemotherapy drugs' side effects and risks (for example, **nausea and vomiting**, some drugs are implicated in causing some cancers), the likelihood of tumor responsiveness needs to be balanced with the patient's quality of life when selecting chemotherapy.

Radiation

Radiation therapy can be effective in the treatment of metastatic disease, especially for metastases to the brain and bones. It is limited, however, because it treats only a limited area. One complication that is possible with radiation therapy is that it has been associated with an increased rate of secondary cancers in patients who have been previously treated for malignancies. The risk is particularly high in patients who were treated with a combination of radiation and chemotherapy.

KEY TERMS

Angiogenesis—The process of forming new blood vessels that supply a tumor with nutrients and help to carry tumor emboli into the larger vessels of the circulatory system.

Apoptosis—The programmed self-destruction of a cell, which takes place when the cell detects some damage to its DNA. Apoptosis is sometimes called "cell suicide."

Basement membrane—A specialized layer of extracellular matrix that separates epithelial tissue from underlying connective tissue. Cancer cells must break through the basement membrane in order to migrate to other parts of the body and form metastases.

Embolus (plural, emboli)—A clump of tumor cells that breaks off from a primary tumor to travel through the circulatory system and lodge in a capillary in another part of the body. The process of forming emboli is called embolization.

Epithelium—The layer of tissue that covers body surfaces and lines the internal surfaces of body cavities, blood vessels, and hollow organs. Most cancer cells arise within epithelial tissue.

Extracellular matrix—A collection of connective tissue proteins and fibers that supports and nourishes body tissues. The extracellular matrix forms a physical barrier to the movement of tumor cells.

Extravasation—The process of reverse invasion in which tumor cells that have invaded the blood vessels and traveled to other organs force their way back out of the blood vessels and into the tissues surrounding their new site.

Micrometastasis (plural, micrometastases)—A term sometimes used to describe malignant tumor cells circulating in the blood or other metastases too small to be detected by a standard clinical examination.

Multicentric—A type of cancer that appears at several different sites in the patient's body simultaneously.

Oncogene—Any gene that is a factor in triggering the development of cancer. Oncogenes are mutated forms of proto-oncogenes, which are genes that promote the normal process of cell growth and division.

Replication—The process in which a cell duplicates or copies itself.

Tumor markers—Substances that occur in the blood, urine, or tissues of patients with certain types of cancer. Tumor markers may be produced either by the tumor itself or by the body in response to the tumor.

Tumor necrosis factor (TNF)—A protein that destroys cells showing abnormally rapid growth. TNF is used in immunotherapy to shrink tumors rapidly.

Tumor suppressor gene—A gene that encodes proteins that inhibit cell division and replication. Tumor suppressor genes are damaged or inactive in many types of cancer cells.

Vascular endothelial growth factor (VEGF)—A substance released by tumor cells that attracts vascular (blood vessel) cells to the tumor. The vascular cells then form new blood vessels within the tumor.

Vascularization—Another name for angiogenesis.

Immunotherapy

Immunotherapy, or immunologic therapy, is a modality, or method, of cancer treatment that is still in its experimental stages. It mobilizes the patient's own immune system to fight cancer cells. Immunotherapy is being evaluated in the treatment of metastatic melanoma, renal cell **carcinoma**, breast tumors, and other tumors. Some of the substances that are being tested in **clinical trials** are produced by the human body, while others are made in laboratories. The major categories of substances used in immunotherapy include:

- **Interferons**. Interferons are proteins produced by virus-infected cells that limit further reproduction of the virus and stimulate resistance to the infection.
- Interleukins. Interleukins are small proteins that promote the growth and activation of the body's white cells. Interleukin-2, known as IL-2 or **aldesleukin**, is approved for the treatment of metastatic melanoma and renal cell carcinoma.
- Tumor necrosis factor (TNF). TNF is a protein that was discovered in 1975. It destroys cells that show unusually rapid growth and stimulates the production of interleukins.

- **Monoclonal antibodies**. Monoclonal antibodies are antibodies produced in laboratory-grown cell clones in order to achieve greater abundance and uniformity than are found in antibodies produced in the body.
- **Vaccines**. Cancer vaccines are intended to stimulate the body's killer T cells (a specialized type of white blood cell) to attack tumor cells. Some vaccines being tested are made from relatively rare white blood cells called dendritic cells; others are made from genetically altered tumor cells.

Newer therapies for metastatic cancer

Recent advances in understanding the process of metastasis have led to some new approaches to treatment.

GENE THERAPY Some researchers are investigating ways to replace a mutated p53 tumor suppressor gene, or to inhibit an activated *ras* oncogene. Another approach involves the use of **angiogenesis inhibitors** to suppress metastatic tumors. An antibody to VEGF, called anti-VEGF, is presently being used in clinical trials for patients with late-stage colon, breast, and lung cancers. A second angiogenesis inhibitor that is being tested is endostatin.

Other researchers are studying substances that trigger apoptosis in defective cells or prevent the uncontrolled multiplication of tumor cells.

ISOLATED PERFUSION Isolated perfusion is the treatment of metastatic melanoma and sarcoma to the extremities by isolating the vasculature (blood vessels) of the affected extremity, and then delivering high doses of chemotherapeutic drugs directly to the area of metastatic disease. The limb is then flushed before re-establishing circulation. With this technique, it becomes possible to deliver doses of drugs regionally that would otherwise be very toxic or lethal if delivered systemically.

HYPERTHERMIA **Hyperthermia** is the use of therapeutic heat to treat cancers on and inside the body. The goal of hyperthermia is to shrink and destroy cancer without harming noncancerous cells. The treatment can be delivered directly to the tumor, to an area of the body, or to the whole body. Research has established that the effectiveness of some forms of radiation therapy and chemotherapy are enhanced when combined with hyperthermia. In 2001, the American Cancer Society acknowledged that hyperthermia could the cells of some cancers more responsive to treatment, but still considered the treatment experimental, especially in whole-body form. The National Institutes of Health are sponsoring ongoing clinical trials studying hyperthermia. Patients with extensive metastasis may not be good candidates for hyperthermia.

Alternative and complementary therapies

The National Center for Complementary and Alternative Medicine (NCCAM) is sponsoring new as well as ongoing trials of alternative treatments for metastatic cancer. One ongoing trial involves **PC-SPES**, a combination of eight Chinese herbs that is used to treat prostate cancer. Other trials are evaluating the use of herbal remedies to treat the side effects of chemotherapy. The National Cancer Institute (NCI) makes information about ongoing clinical trials available. Patients can contact the NCI or the NCCAM at the numbers and web sites listed below.

See also Cancer biology; Cancer genetics; Carcinogenesis; Hepatic arterial infusion.

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"PET Effective in Detecting of Osseous Metastasis from Several Malignancies." *Cancer Weekly* December 30, 2003: 141.

ORGANIZATIONS

American Cancer Society (ACS). 1599 Clifton Road, NE, Atlanta, GA 30329. (404) 320-3333 or (800) ACS-2345. Fax: (404) 329-7530. Web site: <http://www.cancer.org>.

National Cancer Institute, Office of Cancer Communications. 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580.

(800) 4-CANCER (1-800-422-6237). TTY: (800) 332-8615. Web site: <http://www.nci.nih.gov>.

NIH National Center for Complementary and Alternative Medicine (NCCAM) Clearinghouse. P. O. Box 8218, Silver Spring, MD 20907-8218. TTY/TDY: (888) 644-6226. Fax: (301) 495-4957. Web site: <http://www.nccam.nih.gov>.

Office of Cancer Complementary & Alternative Medicine of the National Cancer Institute (OCCAM). Email: ncioccam1-r@mail.nih.gov. Web site: <http://www.occam.nci.nih.gov>.

OTHER

National Center for Environmental Research, U.S. Environmental Protection Agency. Web site: <http://www.es.epa.gov/ncerqa>.

Rebecca J. Frey, Ph.D.
Teresa G. Odle

Methadone *see* **Opioids**

Methotrexate

Definition

Methotrexate is a **folic acid** derivative that interferes with folic acid metabolism (folate antagonist). It is a cytotoxic agent (a chemical that is directly toxic to cells) with multiple characteristics and may be described as an antimetabolite, antineoplastic, and immunosuppressant. In the United States, methotrexate is also recognized by the trade names Folex and Mexate, or the generic name amethopterin.

Purpose

Methotrexate is administered to cancer patients diagnosed with various malignancies. These conditions may include **breast cancer**, lung cancer, non-metastatic bone cancer, cancers associated with the head and neck, **acute lymphocytic leukemia**, meningeal leukemia, advanced **non-Hodgkin's lymphomas**, and uterine tumors. Certain other cancers may be treated with methotrexate as prescribed by the oncologist.

Description

Methotrexate was granted FDA approval in 1986. Methotrexate is a highly effective chemical compound that targets a specific enzyme required by cells for normal function. When this enzyme activity is blocked by methotrexate, certain processes within the cell are shut down and cell death results. The growth of some normal cells may be affected by methotrexate. However, because this is a process associated with actively dividing cells, the accelerated rate at which cancer cells grow and divide make them more susceptible to the effects of methotrexate. Methotrexate may be given as a single agent, often followed by **leucovorin** rescue. Methotrexate may also be administered in a combination regimen with steroids to produce and maintain rapid remission of certain cancers or as part of an adjuvant therapy regimen with **doxorubicin**, **cisplatin**, or the BCD combination of **bleomycin**, **cyclophosphamide**, and **dactinomycin**.

Recommended dosage

Methotrexate is available is both injectable and tablet form. The injectable form may be given intravenously (IV), intramuscularly (IM), or intrathecal (directly into the spinal fluid). The dose amount varies over a wide range for patients receiving methotrexate. The final dose and treatment cycle will be determined by the oncologist based on what the medication is being used for, what cancer type is being treated, whether methotrexate is being used as a single agent or in concert with other anticancer drugs, and the method by which the medication is being administered. It is extremely important to take methotrexate in the correct timetable prescribed by the oncologist. If a dose is missed, the patient should not take the missed dose at a later time, or double the next prescribed dose. Rather, the patient should maintain the schedule prescribed and notify the oncologist about the missed dose.

Precautions

To maximize treatment effects, patients receiving methotrexate should observe certain guidelines. Including any modifications given by the oncologist, these guidelines should include regular visits with the oncologist and laboratory testing for white blood cell count, kidney, liver, and bone marrow function. Avoid any immunizations not approved or prescribed by the oncologist. Avoid contact with individuals taking or that have recently taken oral polio vaccine, or individuals that have an active infection. When necessary wear a protective facemask. Avoid prolonged or direct exposure to sunlight, as some patients experience an increased sensitivity. Ask for specific instructions on oral hygiene procedures to reduce the risk of gum abrasion, and avoid touching the eye and nasal areas unless hands have been properly washed immediately prior to contact. To reduce bleeding and bruising complications, patients should exercise extreme caution when handling sharp instruments and decline participation in contact sports. Prior to treatment, the patient's medical history should be

KEY TERMS

Antimetabolite—Anti-cancer drugs which prevent cells from growing and dividing by blocking the chemical reactions required in the cell to produce DNA.

Antineoplastic—Agents that inhibit or prevent the development of cancers by stopping the maturation and proliferation of malignant cells.

BCD—The combined chemotherapy treatment of bleomycin, cyclophosphamide, and dactinomycin.

Cytotoxic—Chemicals that are toxic to cells, and prevent their reproduction or growth.

Hodgkin's lymphoma—A human malignant disorder of lymph tissue that appears to originate in a particular lymph node and later spreads to the spleen, liver, and bone marrow.

Immunosupressant—Any chemotherapeutic agent which also has the effect of suppressing the immune system.

Leucovorin—The antidote for high dose treatments of methotrexate.

Lymphocytic leukemia—An acute form of childhood leukemia characterized by the development of abnormal cells in the bone marrow and lymph cells found in blood-forming tissues.

Metastatic—Refers to the spread of a cancer from its place of origin to another site in the body.

Oncologist—A physician who specializes in the diagnosis and treatment of patients with cancer.

thoroughly reviewed to avoid complications that might arise from previous conditions such as gout, kidney stones or kidney disease, liver disease, chickenpox, shingles, intestinal blockage, colitis, immunosupression, stomach ulcers, mouth sores, or a history of allergic reactions to various drugs. The oncologist should also be made aware if the patient is pregnant or if there is the possibility the patient might be pregnant, or if the patient is a breast-feeding mother. Only prescribed medications or over the counter (OTC) drugs approved by the oncologist should be taken by a patient receiving methotrexate.

Side effects

The beneficial effects of methotrexate are usually accompanied by less desirable side effects. Side effects correlate in severity with dose amount and length of treatment. It is important to encourage the patient to discuss any presenting side effects. Some side effects do not require medical attention, but still cause the patient concern. Side effects that fall into this category may include loss of hair (alopecia) and appetite (anorexia), nausea or vomiting, skin rash with **itching**, pale skin tone, and the appearance of boils or acne. These side effects tend to diminish as the body adjusts to the therapy, or if they become bothersome, the oncologist may prescribe interventions. Side effects that should be reported immediately to the oncologist include mouth sores; back, lower side, joint or stomach pain; **fever** or chills; headaches; bloody or dark urine; drowsiness; dizziness; black tarry stools; bloody stools or vomit; **diarrhea**; redness or pinpoint red spots on the skin; swelling of the feet or lower legs; the development of a cough or hoarseness; and shortness of breath.

Interactions

Anti-inflammatory medications should be avoided while the patient is receiving methotrexate. These drugs elevate the effects of methotrexate to potentially harmful levels. **Vaccines** should be avoided due to the immunosuppression action of methotrexate, and alcohol should be avoided to reduce the risk of liver complications.

Jane Taylor-Jones, Research Associate, M.S.

Methylphenidate

Definition

Methylphenidate is a mild central nervous system stimulant. This drug is sold under the brand name Ritalin in the United States.

Purpose

Methylphenidate can be used to decrease sedation and lethargy from opioid pain medications. In addition, methylphenidate may improve the mood of a cancer patient suffering from feelings of **depression**, often raises a patient's energy level, and may improve his or her appetite. This drug is also used to treat attention deficit disorder in children and the sleep disorder narcolepsy.

Description

Exactly how methylphenidate acts in the brain is not clear. It is believed to trigger arousal systems or increase the release of brain chemicals. It produces added alertness.

Recommended dosage

How the patient responds to treatment will determine the recommended dose. The usual dose for adults when methylphenidate is ordered with opiate pain medication is 2.5 mg. to 15 mg., daily or twice per day. This drug should be taken exactly as directed. It can become habit-forming if taken in greater amounts or for longer periods than is necessary. Patients should take the last dose of the day before 6 P.M. to decrease sleep difficulties. Patients should not crush or break this medication. If a dose is missed, the patient should take it as soon as possible. Patients should not take two pills at the same time.

Precautions

Methylphenidate can produce physical and mental dependence. Patients should not suddenly stop taking it. A sudden discontinuation of the drug can cause withdrawal symptoms, including depression, paranoid feelings, thoughts of suicide, anxiety, agitation, and sleep disturbances.

Methylphenidate should not be given to patients with extreme anxiety, tension, agitation, severe depression, instability, or a history of alcohol or drug abuse. It is not indicated for use in those with Tourette's syndrome, people with tics, glaucoma, or some mental-health conditions. This drug should be used cautiously in patients with high blood pressure, those with a history of seizures, and women who are breastfeeding. Methylphenidate is not typically ordered for women during their childbearing years, unless the doctor determines that the benefits outweigh the risks. Methylphenidate should not be ordered for patients less than six years of age. Its safety has not been determined in this age group.

Side effects

The most common side effects are nervousness, sleep difficulties, a rapid heartbeat, and increased blood pressure. Reducing the dose or changing the time the drug is taken may reduce some side effects. Patients should discuss any adverse reactions with their doctors. Patients should receive regular blood pressure and pulse checks while on this drug. Methylphenidate also may cause dizziness, irritability, vision changes, drowsiness, and a poor appetite. Patients may experience chest pain, palpitations, joint pain, skin rash, and uncontrolled movements or speech. Patients may develop a rapid or irregular heartbeat, stomach upset, nausea, headache, blood in the urine or stools, muscle cramps, red dots on the skin, or bruises. Patients should not drive or operate machinery or appliances until they understand how this drug affects them. Patients should not drive if they become lightheaded or dizzy. Methylphenidate may cause irregularities in the makeup of the blood and produce changes in liver function. Patients should receive regular blood work.

At higher doses or with long-term use, patients may experience confusion, false beliefs, mood changes, hallucinations, feelings that they or their environment are not real, and **weight loss**.

KEY TERMS

Narcolepsy—Disorder that causes people to suddenly fall asleep

Opiate—Remedy containing or derived from opium, or any drug that induces sleep

Interactions

Several drugs may interfere with methylphenidate, including anticoagulants (blood thinners), and drugs to prevent seizures, combat depression and treat high blood pressure.

Debra Wood, R.N.

Methylprednisolone *see* **Corticosteroids**

Metoclopramide

Definition

Metoclopramide (Reglan, Octamide, Maxeran) is a drug used to prevent the **nausea and vomiting** caused by cancer **chemotherapy**, diabetic neuropathy, gastroesophageal reflux, and similar conditions. It has also been approved by the Food and Drug Administration (FDA) to treat the small bowel prior to intubation. Metoclopramide is one of the drugs most frequently used in palliative care for cancer patients.

Purpose

Nausea and vomiting are among the most common side effects of cancer chemotherapy. They are also among the most unpleasant and upsetting side effects for patients. If left untreated, persistent nausea and vomiting can lead to dehydration, dental decay, digestive abnormalities, and nutritional deficiencies. In addition, persistent vomiting may force some patients to stop taking their chemotherapy and risk a recurrence of their cancer. It is therefore very important that these symptoms be adequately treated.

The nausea and vomiting that occurs with chemotherapy is often divided into three types: anticipatory, acute, and delayed. Anticipatory nausea and vomiting usually occurs before or during chemotherapy. These symptoms are thought to be caused by anxiety, and often occur in patients who have been previously treated with very toxic chemotherapy. Acute nausea and vomiting occurs within a few minutes to several hours after drug administration and usually stops within 24 hours. Delayed nausea and vomiting occurs several hours after chemotherapy, and can last several days.

Description

For the majority of patients, nausea and vomiting can be successfully treated with antiemetic medication. Metoclopramide is one of the most widely used and effective **antiemetics** for treating the delayed nausea and vomiting caused by chemotherapy. It has been used since the 1980s, and works in two ways. It affects a part of the brain known to trigger vomiting, and also affects the speed of intestinal motion. As a result, the stomach empties into the intestines more quickly, and the contents of the intestines move more quickly in the correct direction.

Metoclopramide is most often used in patients taking **cisplatin** (Platinol) chemotherapy. Cisplatin is used to treat a wide range of cancers including **bladder cancer**, **ovarian cancer** and non-small cell lung cancer. Compared with other cancer chemotherapy, cisplatin is often considered to cause the most severe nausea and vomiting. For 60% to 70% of patients taking cisplatin, however, metoclopramide provides adequate control of nausea and vomiting.

Recommended dosage

Although metoclopramide can be taken either orally or intravenously, cancer patients on chemotherapy usually receive the drug intravenously. Metoclopramide is usually given 30 minutes before chemotherapy, and then two more times after chemotherapy at two hour intervals.

The recommended dose varies from patient to patient, and depends on both the severity of nausea and vomiting, and on the toxicity of the drug. A higher dose will be given to patients with severe symptoms. Higher doses will also be given to patients receiving drugs such as cisplatin that are known to cause severe nausea and vomiting. Some patients receiving cisplatin may be given a combination of three different drugs to help combat their nausea: metoclopramide, **dexamethasone** (Dexone), and **lorazepam** (Ativan). The three work on different areas of the body and produce a greater effect together than they do when given separately.

Precautions

Metoclopramide can cause sleepiness and lack of concentration. Patients should avoid tasks that require mental alertness such as driving or operating machinery. Patients should also be aware that metoclopramide may enhance their response to alcohol and drugs that depress the central nervous system. Because metoclopramide can cause **depression**, patients with a history of serious clinical depression should take this drug only if absolutely necessary.

Metoclopramide can make the symptoms of Parkinson's disease worse, and patients with a history of seizures should not take metoclopramide, because the frequency and severity of the seizures may increase. The drug should also not be used in patients with intestinal problems such as bleeding, tears, or blockages. The safety of metoclopramide for pregnant women or children is unknown. The drug is found in the breast milk of lactating mothers.

Side effects

The most frequent side effects of metoclopramide are restlessness, drowsiness, and fatigue. These occur in about 10% of patients. Less common side effects include insomnia, headache, and dizziness. These occur in only 5% of patients. Feelings of anxiety or agitation may also occur, especially after a rapid intravenous injection of the drug. Some women may experience menstrual irregularities.

Metaclopramide therapy can cause some patients to make abnormal involuntary movements, a condition known as dyskinesia. These reactions are most common in young adults of 18–30 years of age, and often disappear about a day after the patient stops taking the drug. Among geriatric patients, particularly women, dyskinesia sometimes develops when patients stop taking metoclopramide after long term treatment.

Interactions

Patients who are also taking cabergoline (Dostinex), a drug used to treat hormonal problems and Parkinson's disease, should not take metoclopramide. Because metoclopramide affects the functioning of the intestines, it can interfere with the absorption of certain drugs. The effect of digoxin (Lanoxin), for example, may be reduced, whereas the effects of other drugs like aspirin, cyclosporine (Neoral, Sandimmune, SangCya) and tetracycline (Minocin, Vibramycin) may be enhanced.

KEY TERMS

Antiemetic—A drug that prevents nausea and vomiting.

Dyskinesia—A condition that causes a person to make abnormal, involuntary movements.

Palliative care—Care given to relieve pain and other symptoms of a disease but not to cure the disease.

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American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657-3000. <www.ashp.org>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

Alison McTavish, M.Sc.
Rebecca J. Frey, Ph.D.

Mistletoe

Description

Mistletoe is a parasitic evergreen plant that lives on trees such asoak, elm, fir, and apple. The parasitic plant has yellowish flowers, small yellowish green leaves, and waxy white berries. There are many species of this plant in the Viscacea and Loranthacea plant families. European mistletoe (*Viscum album*) and American mistletoe (*Phoradendron leucarpum*) are used as medical remedies. In addition to Europe and North America, mistletoe is also found in Australia and Korea.

Mistletoe berries are poisonous to cats and other small animals. There is, however, some debate about how toxic the berries are to humans, and there is controversy about whether it is safe to use mistletoe as a remedy. Mistletoe is also known as mystyldene, all-heal, bird lime, golden bough, and devil's fuge.

General use

Mistletoe is known popularly as the plant sprig that people kiss beneathduring the Christmas season. That custom dates back to pagan times when, according to legend, the plant was thought to inspire passion and increase fertility.

Over the centuries, mistletoe has acquired a reputation asan all-purpose herbal remedy. In the seventeenth century, French herbalistsprescribed mistletoe for nervous disorders, epilepsy, and the spasms known as the St. Vitus dance.

Mistletoe has also been used in folk medicine as a digestive aid, hearttonic, and sedative. It was used to treat arthritis, hysteria and other mentaldisturbances, **amenorrhea**, wounds, asthma, bed wetting, infection, and to stimulate glands.

For centuries, mistletoe also served as a folk medicine treatment for cancer, and as of early 2005, the plant is sometimes used in Europe to treat tumors. Iscador, an extract of the European mistletoe plant, is said to stimulate the immune system and kill cancer cells. It reportedly reducesthe size of tumors and improves the quality of life. Iscador is one brandname of the mistletoe extract in Europe, and other brand names include Helixorand Eurixor.

Although in alternative medicine mistletoe is viewed as a multipurpose remedy, there is disagreement among medical experts about the safety and effectiveness of this herb. The number of possible interactions with other medications described below indicates that mistletoe should be used with caution.

Preparations

In alternative medicine, the leaves, twigs, and sometimes the berries of mistletoe are used. In Europe, mistletoe remedies range from tea made from mistletoe leaves to injections of Iscador. However, the berries may be poisonous and the herb may cause liver damage.

Since as of 2005 mistletoe has not been tested by the United States Food and Drug Administration (FDA), many experts urge caution until more research is completed.

Home remedies

Mistletoe tea may be an alternative treatment for conditions that include high blood pressure, asthma, epilepsy, nervousness, **diarrhea**, andamenorrhea. The tea is prepared by adding 1 tsp (5 g) of finely cut mistletoe to 1 cup (250 ml) of cold water. The solution is steeped at room temperature for 12 hours and then strained.

Mistletoe wine is prepared by mixing 8 tsp (40 g) of the herb into 34oz (1 L) of wine. After three days, the wine can be consumed. Three to fourglasses of medicinal wine may be consumed each day.

Mistletoe must be stored away from light and kept above a drying agent.

Cancer treatment

Iscador, the European extract, may be injected before surgery for cancers of the cervix, ovary, breast, stomach, colon, and lung. Cancer treatments can take several months to several years. The treatment is given by subcutaneous injection, preferably near the tumor. Iscador may be injected into the tumor, especially tumors of the liver, cervix, or esophagus.

The dosage of Iscador varies according to the patient's age, sex, physical condition, and type of cancer. The treatment usually is given in the morning three to seven days per week. As treatment continues, the dosage may be increased or adjusted.

Advocates of Iscador believe it can stimulate the immune system, kill cancer cells, inhibit the formation of tumors, and extend the survival time of cancer patients. They maintain that mistletoe can help prevent cancer and be complementary to standard medical cancer treatments. They also think that mistletoe could possibly repair the DNA that is decreased by chemotherapy and radiation.

AIDS treatment

Mistletoe extract has been used to combat AIDS, but its efficacy has not been medically confirmed as of 2005.

Precautions

Opinions are sharply divided on how safe and effective the herb is as a home remedy and in the treatment of conditions such as cancer and AIDS. There is controversy about which parts of the plants are poisonous. Although the berries are classified as poisonous in the United States, some sources say that eating berries is only dangerous for babies, and only if handfuls are consumed. Pregnant or breast-feeding women, however, should not use the plant.

According to a report from the Hepatitis Foundation International, mistletoe is toxic to the liver. However, the *PDR for Herbal Medicines* advises that there are no health hazards when mistletoe is taken properly and in designated therapeutic dosages.

People considering mistletoe should consult with their doctors or practitioners. Until there is definitive proof otherwise, there is a risk that the herbal remedies will conflict with conventional treatment.

KEY TERMS

Amenorrhea—Abnormal absence or suppression of menstruation.

Orthostatic—Related to or caused by an upright position.

Pharmacognosist—A person involved in pharmacognosy, the scienceconcerned with the medical products of plants in their natural state.

Subcutaneous—Beneath the skin.

Vertiginous attacks—Attacks of vertigo or dizziness.

Side effects

Mistletoe may be toxic to the liver. For people diagnosed with hepatitis, use of an herb such as mistletoe may cause additional liver damage. However, advocates of mistletoe maintain it is safe, at least under certain circumstances.

Commercial mistletoe extracts may produce fewer side effects. The bodytemperature may rise and there may be flu-like symptoms. The patient may experience nausea, abdominal pain, and (if given the extract injection) inflammation around the injection sight. Allergy symptoms may result.

Interactions

Mistletoe should not be used by people who take monoamine oxidase (MAO) inhibitor antidepressants such as Nardil. Potential reactions include a dangerous rise in blood pressure and a lowering of blood potassium levels (hypokalemia). In addition, mistletoe may interfere with the action of antidiabetic medications, to increase the activity of diuretics, and to increase the risk of a toxic reaction to aspirin or NSAIDs. Cancer patients

considering mistletoe treatment should first consult with their doctors or practitioners.

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National Cancer Institute (NCI). NCI Public Inquiries Office, Suite 3036-A, 6116 Executive Boulevard, MSC8322, Bethesda, MD, 20892.(800)422-6237. <www.nci.nih.gov/cancerinfo/pdq/cam/mistletoe>.

Liz Swain
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Mithramycin *see* **Plicamycin**

Mitoguazone

Definition

Mitoguazone is an investigational (experimental) medicine used to stop growth of cancer and formation of new cancer cells.

Purpose

Mitoguazone may be effective in patients with **acute leukemia**, **chronic myelocytic leukemia**, **lymphoma**, **multiple myeloma**, **head and neck cancers**, **esophageal cancer**, and other types of malignancies.

Description

Mitoguazone, also known as MGBG, was discovered in 1898. The exact mechanism of MGBG action is not fully understood and a variety of mechanisms appear to be involved. Most likely, MGBG's anti-tumor activity comes from inhibition of spermine, a protein necessary for cell reproduction. This drug underwent numerous **clinical trials** in the early 1960s; however, the trials were discontinued due to severe toxicities noticed when MGBG was given on a daily basis. In these early research trials, MGBG was shown to have both anti-cancer and antiviral activity. Later, researchers discovered that MGBG has a long duration of action in the body and can be given less frequently. In 1976 MGBG enjoyed a rebirth when Southwest Oncology Group started using once weekly administration schedule of this agent in patients with lymphoma (Hodgkin's and non-Hodgkin's type), esophageal cancer, **prostate cancer** and other tumor types.

In addition to being effective as a single agent, MGBG was used in combination **chemotherapy** regimens containing **ifosfamide**, **methotrexate** and **etoposide** (also known as MIME regimen). The best results with MGBG have been obtained against Hodgkin's and non-Hodgkin's lymphoma using MIME regimen.

Mitoguazone appears particularly effective in patients who are malnourished and would be ideally suited for patients with AIDS-associated lymphomas. Another potential advantage of mitoguazone in patients with AIDS is its high penetration into the brain, since the brain is one area frequently involved by lymphoma in this patient population.

Recommended dosage

Adults

AIDS-ASSOCIATED NON-HODKIN'S LYMPHOMA Doses vary between different chemotherapy protocols. One of the schedules used was 600 mg per square meter of body surface area given intravenously on days 1, 8, and then every two weeks.

Children

There is no data available on dosing and use of mitoguazone in children.

Precautions

To maximize treatment effects, patients receiving mitoguazone should observe certain guidelines. In

KEY TERMS

AIDS—Also known as acquired immunodeficiency syndrome, caused by the progression of HIV, and is the leading cause of death from HIV. AIDS is characterized by opportunistic diseases, including fungal infections, pneumocystis carinii pneumonia, non-Hodgkin's lymphoma, and other malignant or infectious illnesses.

Non-Hodgkin's lymphoma—Lymphomas are some of the most treatable cancers with cure rates around 50% in 1990s. Non-Hodgkin's lymphoma mainly affects people over 50 years of age and has been more difficult to treat than the Hodgkin's type. There has been an increase in non-Hodgkin's lymphoma cases in the last two decades in patients with HIV.

addition to any modifications given by the oncologist, these guidelines should include regular visits with the oncologist and laboratory testing for white blood cell count, liver, and bone marrow function. Avoid any immunizations not approved or prescribed by the oncologist. When necessary wear a protective facemask. Use good oral hygiene to reduce incidence of mouth sores and avoid touching the eye and nasal areas unless hands have been properly washed immediately prior to contact. To reduce bleeding and bruising complications, patients should exercise extreme caution when handling sharp instruments and decline participation in contact sports. Prior to treatment, the patient's medical history should be thoroughly reviewed to avoid complications that might arise from previous conditions such as liver disease, chickenpox, shingles, peripheral **neuropathy** (tingling and weakness in hands or feet), suppressed immune system, stomach ulcers, mouth sores, or a history of allergic reactions to various drugs.

Contact a doctor immediately if any of these symptoms develop:

- signs of infection (**fever**, chills, sore throat)
- pain, numbness, and tingling in fingers or toes
- severe muscle weakness
- nausea, vomiting, and yellowing of the skin or eyes
- unresolved mouth sores
- mental status changes (euphoria, drowsiness, anxiety, emotional instability)
- unusual bleeding or bruising
- skin rash or itching

Side effects

The dose-limiting toxicity of MGBG is muscle weakness. The most common side effect of MGBG is flushing primarily on the face during infusion. Other toxicities associated with MGBG are usually mild, consisting of somnolence, tingling in the face or extremities, ringing in the ears, euphoria, mouth ulcers, nausea, vomiting, and **fatigue**. This drug also lacks significant **myelosuppression**, which makes it an ideal agent to consider for combination regimens.

Interactions

The drug and food interactions with MGBG have not been studied in research trials. There is a theoretical drug interaction between MGBG and pentamidine (a drug used to prevent and treat pneumocystis carinii **pneumonia** in AIDS patients). Pentamidine inhibits the same enzyme in the body as MGBG, which can enhance effects of MGBG. This interaction can either increase effectiveness of MGBG against cancer or put patients at higher risk of its side effects.

Olga Bessmertny, Pharm.D.

Mitomycin-C

Definition

Mitomycin-C is also known as mitomycin and MMC. It is an antineoplastic, or medicine that kills cancer cells. It is sold under the trade name Mutamycin.

Purpose

Mitomycin-C may be used to fight a number of different cancers, including cancer of the stomach, colon, rectum, pancreas, breast, lung, uterus, cervix, bladder, head, neck, eye, and esophagus.

It is impossible to provide a detailed description of how mitomycin-C may be combined with other medications in the treatment of each of these cancers, but some examples can be presented. In the treatment of non-small cell lung cancer (NSCLC), one therapeutic regimen that may be used is known as MT, which consists of mitomycin-C, **vindesine**, and **cisplatin**.

Mitomycin-C is sometimes used in patients with colorectal cancer metastatic to the liver. However, the side effects of mitomycin-C, especially those involving the bone marrow and **fatigue**, are so great that other medications may be tried first. In treating breast cancer

metastatic to the liver, mitomycin is regarded as salvage therapy as of the early 2000s.

For advanced stomach cancer, the FAM regimen may be used, which consists of **fluorouracil**, **doxorubicin** (adriamycin), and mitomycin-C. Mitomycin-C may also be used for colorectal cancer metastatic to the liver in combination with other medicines.

More recently, mitomycin has been found effective in treating malignant melanoma of the eye.

In addition to cancer treatment, mitomycin is sometimes used as a topical application in eye surgery to prevent visual haze after operations on the cornea (the transparent exterior coat that covers the front of the eye where light enters). It is also used topically by some doctors to keep incisions in the ear drum open in children with recurrent ear infections without the need to place ventilation tubes in the incisions. This use of mitomycin is considered experiental as of 2005.

Description

Mitomycin-C is an antitumor antibiotic. Mechanistically however, it belongs to DNA covalent binding (alkylating) agents. Mitomycin-C, upon bioactivation, kills cancer cells by disrupting the activity of DNA within the cells. DNA is an acid that contains genetic material.

Recommended dosage

Twenty milligrams per square meter should be given intravenously every six to eight weeks when this medication is used alone. Alternately, five to ten milligrams per square meter may be given every six weeks when the drug is used in combination with other drugs. Mitomycin-C, **leucovorin**, and fluorouracil may be used to treat metastatic **rectal cancer**; this regimen includes an injection of 10 milligrams per square meter of mitomycin-C. When mitomycin-C is combined with vindesine and cisplatin in the treatment of non-small cell lung cancer, eight milligrams per square inch are administered intravenously on days one and twenty-nine of a six-week cycle.

Precautions

Because of the side effects associated with mitomycin-C, some physicians perform blood tests and order chest x rays (of the lungs) for patients receiving this therapy. The likelihood that lung problems will appear in patients receiving mitomycin-C increases if oxygen therapy and/or x-ray therapy are administered.

Patients receiving less than 60 mg of mitomycin-C are at reduced risk of developing a complex medical condition called cancer-associated hemolytic uremia syndrome (HUS). HUS is characterized by **anemia**, other blood defects, and kidney problems. Doctors should carefully observe patients receiving mitomycin-C, as cancer-related HUS is best treated early. However, HUS is not likely to develop until four or more months after the patient received the final dose of mitomycin-C. To achieve early diagnosis of HUS, the doctor may carefully monitor kidney function and blood levels. In addition, transfusions may be avoided as may be certain other procedures involving the blood, as these may increase the risk HUS will develop.

KEY TERMS

Antineoplastic—A medicine given to kill cancer cells.

Salvage therapy—A term that refers to measures taken at a late point in the treatment process after other therapies have failed.

Topical—Referring to a medication or other preparation applied directly to the skin or other external body tissues.

Side effects

The ability of the bone marrow to produce blood cells may be affected. This side effect can be serious. If it occurs, the doctor may decide to reduce the dose of medicine administered. However, mitomycin-C may cause delayed, rather than immediate, bone marrow suppression. Once such suppression does occur it may last for as many as eight weeks.

Major lung problems may occur. Such lung deficits may start as no more than cough, fatigue, and breathing problems. Doctors may conduct lung function tests and obtain x rays to observe whether lung problems are developing. If these lung problems do occur, **corticosteroids** may provide effective therapy. Stopping mitomycin-C therapy may also be recommended.

Mitomycin-C may also cause cancer-associated HUS.

In addition, there may be **nausea and vomiting**, loss of appetite (anorexia), stomach problems, fatigue, **fever**, hair loss (alopecia), and lung problems. If bleeding does occur, there may be damage to the surrounding skin.

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United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

Bob Kirsch
Rebecca J. Frey, PhD

Mitotane

Definition

Mitotane (also known by the brand name Lysodren) is a medicine that has been proven to be effective in the treatment of adrenocortical carcinoma.

Purpose

Mitotane destroys cells of the adrenocortex. The adrenocortex, also called the adrenal cortex, is a section of adrenal gland that sits on top of the kidneys. Mitotane is usually used for patients whose cancer cannot be treated surgically and for patients whose cancer has metastasized.

KEY TERMS

Adrenocortex—The outer part of adrenal gland that sits on top of the kidneys.

Anorexia—A condition of uncontrolled lack or loss of desire for food.

Description

As a chemical, mitotane resembles the insecticides DDD and DDT, although mitotane does not harm people as these do. Scientists do not understand why, but the drug causes damage to the adrenocortex in such a way as to be helpful for some patients with adrenocortical tumors. In addition, mitotane restricts the ability of the gland to produce chemicals.

Recommended dosage

The dose of mitotane given to patients varies, although between four and eight grams (0.12–0.25 oz) per day is a typical dose. Patients vary in how much mitotane they tolerate, some patients tolerating two grams (0.1 oz) per day while others tolerate sixteen grams (0.5 oz) per day. The doses are given orally. At the beginning of the therapy, the patient may receive 500 milligrams of mitotane twice a day. At any one time a third or a quarter of an entire day's dose is taken. If the patient has difficulty tolerating a certain dose, the doctors may adjust this and use a somewhat smaller dose. Mitotane should be given for at least three months. If the medicine is effective, it may be continued indefinitely. However, most patients respond to the x-ray treatment of the pituitary gland and so do not need mitotane treatment to continue indefinitely.

Many doctors use mitotane in conjunction with **radiation therapy** directed to the pituitary gland, but other approaches to this medicine may also be taken.

Precautions

Many patients on mitotane should receive adrenocorticosteroids.

Side effects

Four out of five patients receiving mitotane experience **anorexia** and nausea. About one-third of patients

experience lethargy and sleepiness. Roughly one in five develop skin problems with the medicine. However, patients who experience these side effects do not have to stop taking the medication, although the doctor may lower the dose the person is receiving.

Interactions

Mitotane should not be given with spironolactone (a diuretic/water pill).

Bob Kirsch

Mitoxantrone

Definition

Mitoxantrone, also known by its trade name Novantrone, is an anticancer agent effective against certain kinds of leukemias. It is also used in Multiple Sclerosis (MS), and was approved by the Federal Drug Administration in 1987.

Purpose

Mitoxantrone is used with other drugs to treat acute non-lymphocytic leukemia (ANLL), a category that includes myelogenous, promyelocytic, monocytic and erythroid **acute leukemia**. In adults, ANLL accounts for up to 85% of all adult leukemia cases. Mitoxantrone may also be used in the treatment of acute lymphocytic leukemia, chronic myelocytic leukemia, **ovarian cancer**, advanced or recurrent **breast cancer**, **prostate cancer**, and MS.

Description

Mitoxantrone is classified as an anthracycline antitumor antibiotic, and closely resembles another drug in this category, **daunorubicin**. Although its precise mechanism is not clear, mitoxantrone is cell cycle non-specific, meaning that it is toxic to cells that are dividing, as well as those that are not.

Recommended dosage

Mitoxantrone is given intravenously over a thirty-minute time period. **Chemotherapy** dosages are based on a person's body surface area (BSA), which is calculated in square meters using height and weight measurements. Drug dosages are ordered in milligrams per square meter (mg/m^2).

In patients with cancer, the recommended dosage for induction therapy is 12mg/ mg/m^2 administered on the first three days of treatment. After that time, another chemotherapy drug is usually infused. This course of treatment is often adequate to induce remission, but may be repeated if it does not. In the second induction course, the dosage remains the same, but mitoxantrone is given for two days, rather than three, followed by other chemotherapy agents. Dosages may be altered, depending on the level of bone marrow toxicity the patient develops.

For patients with solid tumors, such as advanced hormone-refractory prostate cancer, a single dose of 12mg/ mg/m^2 is administered, and repeated every three to four weeks. Recent studies show that mitoxantrone used with glucocorticoids has resulted in improved pain control and quality of life in men with prostate cancer.

Precautions

Mitoxantrone's use in children has not been studied sufficiently to determine whether its use is safe and effective. It should not be used in individuals who have experienced a previous reaction to it.

Mitoxantrone is excreted by the liver and kidneys. It may alter the appearance of urine, causing it to be a blue-green color for approximately 24 hours. The sclera, or whites of the eyes, may temporarily be blue-tinged. Patients should not be alarmed by this change, but should alert their doctors if it is prolonged or is accompanied by other symptoms.

Mitoxantrone should not be administered to pregnant women, as damage to the fetus may occur. Throughout treatment, women should use methods to prevent pregnancy. It is excreted in breast-milk, so breast-feeding should be avoided during treatment.

Side effects

Mitoxantrone can cause severe and sometimes rapid **myelosuppression** leading to decreased white blood cell, red blood cell, and platelet counts. Blood counts should be monitored frequently throughout treatment. The white blood cells tend to nadir, or drop to their lowest point, within ten to fourteen days after mitoxantrone is administered. Patients should also be examined for symptoms of low white blood cell count, which typically resemble those of an infection: sore throat, burning with urination, increased temperature, or swelling. Patients should also be carefully monitored for indications that platelet count is low. Symptoms may include unexplained bruises, bleeding or increased bleeding with menstruation, and headache.

KEY TERMS

Body surface area (BSA)—A measurement, based on a patient's height and weight, that helps determine appropriate chemotherapy dosages.

Mucositis—A severe, painful inflammation of the mucous membranes.

Myelosuppression—A condition in which bone marrow activity is diminished, resulting in decreased platelet, red blood cell, and white blood cell counts.

Remission—The time period during which symptoms of a disease are absent.

Mitoxantrone can damage the heart, possibly causing changes that lead to congestive heart failure (CHF). Patients especially at risk are those previously treated with anthracyclines or radiation to the chest area, or those with an already existing heart condition. Symptoms to watch for include swelling of the hands and ankles, difficulty breathing, or heart palpitations.

Mitoxantrone can cause a severe, painful inflammation of the mucous membranes called **mucositis**. The condition may develop within a week of treatment. A patient may experience a burning sensation in his or her throat, as well as mouth pain. Mucositis typically resolves in a few weeks on its own, but there are measures one can take to hasten the process and provide comfort during healing. Hydration is very important to keep the mouth moist. Good oral hygiene is important—the teeth should be brushed with a very soft toothbrush, and flossed gently with unwaxed dental floss. (If bleeding occurs, using a toothbrush may not be safe. Patients should talk to their health care providers should this occur.) Your doctor or nurse may recommend a special mouthwash that helps relieve pain.

Patients undergoing treatment with mitoxantrone may be at risk for **tumor lysis syndrome**, a potentially life-threatening condition that develops when large numbers of cells rupture and release their contents into the blood stream. Preventative measures should be implemented to prevent adverse effects.

Interactions

Because mitoxantrone can alter normal blood counts, medications that contain aspirin should be avoided. Aspirin acts as a blood-thinner, and can predispose a person to bleeding. Patients should discuss all medications, whether they are prescribed or over-the-counter drugs, with their doctor to ensure there are no potential interactions. **Cytarabine**, another drug used to treat cancer, may increase the toxicity of mitixantrone if the drugs are used together.

Tamara Brown, R.N.

MMPI's *see* **Matrix metalloproteinase inhibitors**

Mohs' surgery

Definition

Mohs' surgery, also called Mohs' micrographic surgery, is a precise surgical technique that is used to remove all parts of cancerous skin tumors while preserving as much healthy tissue as possible. It is named for Frederic Edward Mohs, an American surgeon (1910–).

Purpose

Mohs' surgery is used to treat such skin cancers as **basal cell carcinoma**, **squamous cell carcinoma of the skin**, **melanoma**, Bowen's disease, extramammary Paget's disease, **leiomyosarcoma**, **laryngeal cancer**, **malignant fibrous histiocytoma**, microcystic adnexal carcinoma, mucoepidermoid carcinoma, and **Merkel cell carcinoma**.

Malignant skin tumors may appear as strange-looking asymmetrical shapes. The tumor may have long finger-like projections that extend across the skin (laterally) or down into the skin. Because these extensions may be composed of only a few cells, they cannot be seen or felt. Standard surgical removal (excision) may miss these cancerous cells leading to recurrence of the tumor. To assure removal of all cancerous tissue, a large piece of skin needs to be removed. This causes a cosmetically unacceptable result, especially if the cancer is located on the face. Mohs' surgery enables the surgeon to precisely excise the entire tumor without removing excessive amounts of the surrounding healthy tissue.

Precautions

To reduce the risk of bleeding, the use of nonsteroidal anti-inflammatory medications, alcohol, vitamin E, and fish oil tablets should be avoided prior to the procedure. Patients who use the anticoagulants aspirin, coumadin, or **heparin**, should consult with the prescribing physician before changing their use of these drugs.

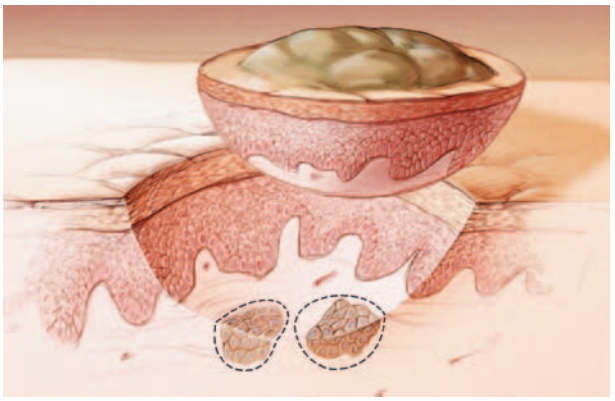
KEY TERMS

Debulking—The removal of the major portion of a tumor by surgery so that the remainder of the tumor can be treated more effectively, usually by chemotherapy or radiation therapy.

Fixative—A chemical that preserves tissue without destroying or altering the structure of the cells.

Fixed—A term used to describe chemically preserved tissue. Fixed tissue is dead so it does not bleed or sense pain.

Mohs' excision—Referring to the excision of one layer of tissue during Mohs' surgery. Also called stage.



Mohs' surgery is used to remove skin cancer tumors of many types, including melanoma. Here, the main portion of the tumor is excised (debulked) using a spoon-shaped tool (curette). Further layers of tissue will be removed as necessary. *(Custom Medical Stock Photo. Reproduced by permission.)*

Description

There are two types of Mohs' surgery: fresh-tissue technique and fixed-tissue technique. Seventy-two percent of surgeons who perform Mohs' surgery use only the fresh-tissue technique. The remaining surgeons use both techniques; however, the fixed-tissue technique is used in fewer than 5% of the patients. The main difference between the two techniques has to do with the preparation steps.

Fresh-tissue technique

Fresh-tissue Mohs' surgery is performed under local anesthesia for tumors of the skin. The area to be excised is cleaned with a disinfectant solution and a sterile drape is placed over the site. The surgeon may outline the tumor using a surgical marking pen or a dye. A local anesthetic (lidocaine plus epinephrine) is injected into the area. Once the local anesthetic has taken effect, the main portion of the tumor is excised (debulked) using a spoon-shaped tool (curette). To define the area to be excised and allow for accurate mapping of the tumor, the surgeon makes identifying marks around the wound. These marks may be made with stitches, staples, fine cuts with a scalpel, or temporary tattoos. One layer of tissue is carefully excised (first Mohs' excision), cut into smaller sections, and taken to the laboratory for analysis.

If cancerous cells are found in any of the tissue sections, a second layer of tissue is removed (second Mohs' excision). Because only the section(s) that have cancerous cells are removed, healthy tissue can be spared. The entire procedure, including surgical repair of the wound, is performed in one day. Surgical repair may be performed by the Mohs' surgeon, a plastic surgeon, or other specialist. In certain cases, wounds may be allowed to heal naturally.

Fixed-tissue technique

With fixed-tissue Mohs' surgery, the tumor is debulked as described above. Trichloracetic acid is applied to the wound (to control bleeding) followed by a preservative (fixative) called zinc chloride. The wound is dressed and the tissue is allowed to fix for 6 to 24 hours, depending on the depth of the tissue involved. This fixation period is painful. The first Mohs' excision is performed as above; however, anesthesia is not required because the tissue is dead. If cancerous cells are found, fixative is applied to the affected area for an additional 6 to 24 hours. Excisions are performed in this sequential process until all cancerous tissue is removed. Surgical repair of the wound may be performed once all fixed tissue has sloughed off, usually a few days after the last excision.

Preparation

Under certain conditions, such as the location of the skin tumor or health status of the patient, **antibiotics** may be taken prior to the procedure (prophylactic antibiotic treatment). Patients are encouraged to eat prior to surgery and bring along snacks in case of a lengthy procedure.

Aftercare

Patients should expect to receive specific wound care instructions from their physicians or surgeons, but

QUESTIONS TO ASK THE DOCTOR

- How long have you been performing Mohs' surgery?
- Will you use the fresh-tissue or fixed-tissue technique?
- Will I have to alter the use of my current medications for this procedure?
- What will you do if you don't find the border of the cancerous lesion?
- How will the wound be repaired?
- Will I need a plastic surgeon to repair the wound?
- What is the cure rate for this type of cancer when treated by Mohs' surgery?
- What is the chance that the tumor will recur?
- How often will I have follow-up appointments?

generally, wounds that have been repaired with absorbable stitches or skin grafts are kept covered with a bandage for one week. Wounds that were repaired using nonabsorbable stitches are covered with a bandage, which should be replaced daily until the stitches are removed one to two weeks later. Patients with nonabsorbable stitches may shower. Signs of infection (e.g., redness, pain, drainage) should be reported to the physician immediately.

Risks

Using the fresh-tissue technique on a large tumor requires large amounts of local anesthetic, which can be toxic. Complications of Mohs' surgery include infection, bleeding, scarring, and nerve damage.

Normal results

Mohs' surgery provides high cure rates for malignant skin tumors. For instance, the five-year cure rate for basal cell carcinoma treated by Mohs' surgery is greater than 99%. The frequency of recurrence is much lower with Mohs' surgery (less than 1%) than with conventional surgical excision.

Abnormal results

Tumors spread in unpredictable patterns. Sometimes a seemingly small tumor is found to be quite large and widespread, resulting in a much larger excision than was anticipated. Technical errors, such as those involving processing and interpretation of the tissue sections, may lead to local recurrence of cancer.

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Monoclonal antibodies

Definition

Monoclonal antibodies are proteins produced in the laboratory from a single clone of a B cell, the type of cells of the immune system that make antibodies.

Description

Antibodies, also known as immunoglobulins (Igs), are proteins that help identify foreign substances to

the immune system, such as a bacteria or a virus. Antibodies work by binding to the foreign substance to mark it as foreign. The substance that the antibody binds to is called an antigen. All monoclonal antibodies of a particular type bind to the same antigen, which distinguishes them from polyclonal antibodies.

The structure of most antibodies can be divided into two parts: the section that binds the antigen and a section that identifies the type of antibody. This second region is called a constant region, because it is essentially the same within the same type of antibody. The most common type of antibody is IgG (immunoglobulin gamma), which is found in the blood and body fluids. For cancer treatments, monoclonal antibodies are often humanized. This involves using human sequences for the constant regions and using mouse or other animal-derived sequence for the binding region. Humanization reduces the immune reaction of the patient to the antibody itself.

When used as a treatment for cancer, there are three general strategies with monoclonal antibodies. One uses the ability of the antibodies to bind to the cancer cells having the tumor antigens on their surface. The immune system will see the cancer cells marked with bound antibodies as foreign and destroy them. A second strategy is to use the antibodies to block the binding of cytokines or other proteins that are needed by the cancerous cells to maintain their uncontrolled growth. Monoclonal antibodies designed to work like this bind to the receptors for the cytokine that are on the tumor cell surface. As doctors don't completely understand how monoclonal antibodies work as drugs, both strategies may help rid the body of the tumor cells.

A final strategy involves special antibodies that are linked (conjugated) to a substance that is deadly to the cancer cells. Both radioactive isotopes, like yttrium 90, and toxins produced by bacteria, like pseudomonas exotoxin, have been successfully conjugated to antibodies. The antibodies are then used to specifically destroy the tumor cells with the radioactivity or toxic substance. The use of monoclonal antibodies is a useful approach to cancer therapy and as scientists learn more about the function of the immune system and cancer, new antibodies and new strategies promise to become more and more effective.

Michelle Johnson, M.S., J.D.

Morphine *see* **Opioids**

MRI *see* **Magnetic resonance imaging**

Mucositis

Description

Mucositis involves the inflammation of the lining of the mouth and digestive tract, and frequently occurs in cancer patients after **chemotherapy** and radiation therapy. The cheek, gums, soft plate, oropharynx, top and sides of tongue, and floor of the mouth may be affected, as well as the esophagus and rectal areas. Along with redness and swelling, patients typically experience a strong, burning pain.

Although there are factors that increase the likelihood and severity of mucositis, there is no reliable manner to predict who will be affected. Not only is mucositis more common in elderly patients, the degree of breakdown is often more debilitating. The severity of mucositis tends to be increased if a patient exercises poor oral hygiene or has a compromised nutritional status. A pre-existing infection or irritation to the mucous membrane may also result in a more severe case of mucositis.

Causes

The precise mechanism by which cancer treatment induces mucositis is not clear, but it is believed to damage the rapidly dividing epithelial cells in the mucous membranes. This damage leads to inflammation and swelling, and then actual breakdown of the mucosa, the lining of the mouth and digestive tract. Another theory is that the body's natural defenses are weakened. For example, the immunoglobulin IgA is normally found in saliva. In patients who developed mucositis after undergoing cancer treatment with **methotrexate**, IgA levels in saliva were decreased.

The types of drug used to treat cancer and the schedule by which they are given influence the risk of developing mucositis. **Doxorubicin** and methotrexate, for example, frequently cause mucositis. The chemotherapy agent **fluorouracil** does not usually severely affect the mucous membranes when administered in small doses over continuous intravenous (IV) infusion. When the schedule is adjusted so that a higher dose is given over a shorter period of time (typically over five days), fluorouracil can cause very severe, painful, dose-limiting cases of mucositis. Patients undergoing treatment with high-dose chemotherapy and bone marrow rescue usually develop mucositis.

In addition, mucositis also tends to develop in **radiation therapy** administered to the oral cavity, or in dosages that exceed 180 cGy per day over a five-day period. Combination therapy, either multiple chemotherapy agents or chemotherapy and radiation therapy to the oral cavity, can increase the incidence of mucositis.

Treatments

Because there is no real cure for mucositis, treatment is aimed at prevention and management of symptoms. Mucositis typically resolves a few weeks after treatment as the cells regenerate, and treatment cessation is only occasionally required. In some cases, drug therapy will be altered so that a less toxic agent is given.

Patients at risk for mucositis should be meticulous about their oral hygiene, brushing frequently with a soft toothbrush and flossing carefully with unwaxed dental floss. If bleeding of the gums develops, patients should replace their toothbrushes with soft toothettes or gauze. Dentures should also be cleaned regularly. Patients should be well-hydrated, drinking fluids frequently and rinsing the mouth several times a day. Mouthwashes that contain alcohol or hydrogen peroxide should be avoided as they may dry out the mouth and increase pain. Lips should also be kept moist. Physical irritation to the mouth should be avoided. If time permits, dental problems, such as cavities or ill-fitting dentures, should be resolved with a dentist prior to beginning cancer treatment. Patients are generally more comfortable eating mild, medium-temperature foods. Spicy, acidic, very hot or very cold foods can irritate the mucosa. Tobacco and alcohol should also be avoided.

Hospital personnel and the patients themselves should inspect the mouth frequently to look for signs and symptoms of mucositis. Evidence of mucositis (inflammation, white or yellow shiny mucous membranes developing into red, raw, painful membranes) may be present as early as four days after chemotherapy administration.

Sodium bicarbonate mouth rinses are sometimes used to decrease the amount of oral flora and promote comfort, though there is no scientific evidence that this is beneficial. Typically, patients will rinse every few hours with a solution containing 1/2 teaspoon (tsp) salt and 1/2 tsp baking soda in one cup of water.

Pain relief is often required in patients with mucositis. In some cases, rinsing with a mixture of maalox, xylocaine, and **diphenhydramine** hydrochloride relieves pain. However, because of xylocaine's numbing effects, taste sensation may be altered. Worse, it may reduce the body's natural gag reflex, possibly causing problems with swallowing. Coating agents such as kaopectate and aluminum hydroxide gel may also help relieve symptoms. Rinsing with benzydamine has also shown promise, not only in managing pain, but also in preventing the development of mucositis. More severe pain may require liquid tylenol with codeine, or even intravenous opioid drugs. Patients with severe pain may not be able to eat, and may also require nutritional supplements through an I.V. (intravenous line).

KEY TERMS

Combination therapy—Treatment involving multiple drugs or treatment methods.

Mucosa—The lining of the mouth and digestive tract.

Alternative and complementary therapies

A treatment called **cryotherapy** has shown promise in patients being treated with fluorouracil administered in the aforementioned five-day, high-dose schedule. Patients continuously swish ice chips in their mouth during the thirty-minute infusion of the drug, causing the blood vessels to constrict, thereby reducing the drug's ability to affect the oral mucosa.

Chamomile and **allopurinol** mouthwashes have been tried in the past to manage mucositis, but studies have found them to be ineffective. Biologic response modifiers are being evaluated to determine their possible role in managing mucositis. Recent studies using topical antimicrobial lozenges have shown promise as well, but more research is needed.

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Tamara Brown, R.N.

Multiple endocrine neoplasia syndromes

Definition

The multiple endocrine neoplasia (MEN) syndromes are three related disorders in which two or more of the hormone-secreting (endocrine) glands of the body develop tumors. Commonly affected glands are the thyroid, parathyroids, pituitary, adrenals, and pancreas. Two common cancers are medullary **thyroid cancer** and gas-

trinomas. MEN is sometimes called familial multiple endocrine neoplasia (FMEN) and previously has been known as familial endocrine adenomatosis.

Description

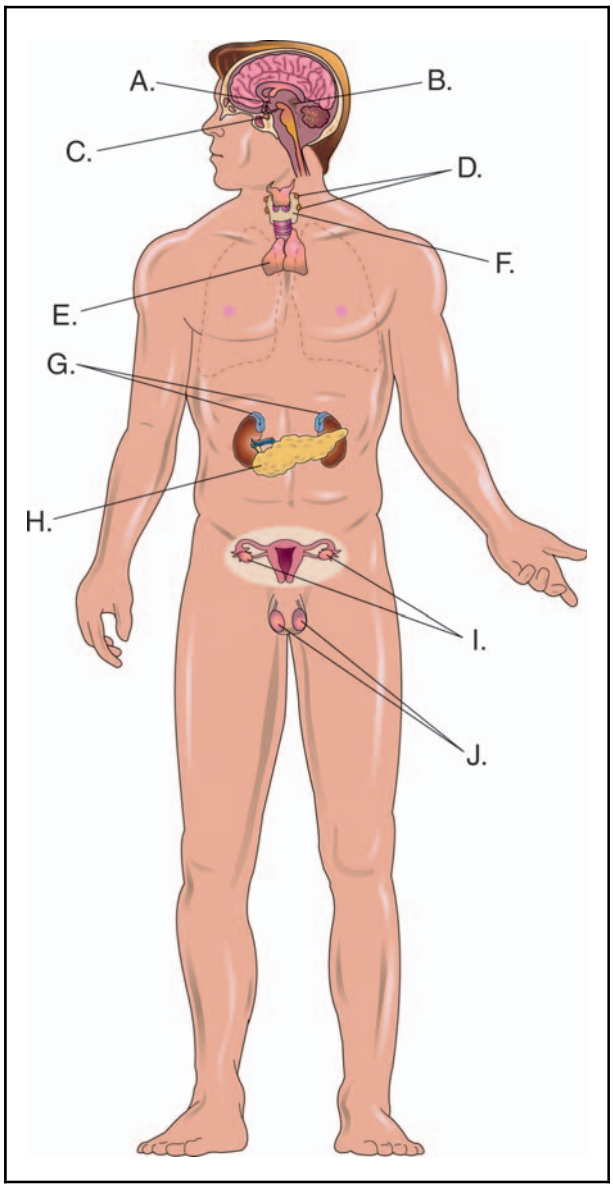
The three forms of MEN are MEN1 (Wermer's syndrome), MEN2A (Sipple syndrome), and MEN2B (previously known as MEN3). Each form leads to excessive growth of normal cells (hyperplasia) and overactivity of a number of endocrine glands. Excessive growth can result in the formation of tumors (neoplasia) that are either benign (noncancerous) or malignant (cancerous). Overactive endocrine glands increase the secretion of hormones into the bloodstream. Hormones are important chemicals that control and instruct the functions of different organs. Their levels in the body are carefully balanced to maintain normal functioning of many vital processes, including metabolism, growth, timing of reproduction, and the composition of blood and other body fluids.

All three forms are genetic disorders. They result when an abnormal form of a gene is inherited from one parent. The gene causing MEN1, named the MEN1 gene, was isolated in 1997. Both types of MEN2 are caused by mutations of the RET (REarranged during Transfection) gene. MEN1 and MEN2 are both autosomal dominant genetic conditions, meaning that an individual needs only one defective copy of the MEN1 gene or the RET gene to develop the associated disorder. In all forms, the children of an affected individual have a 50% chance of inheriting the defective gene.

The three forms of MEN are further distinguished by the endocrine glands affected. MEN1 is characterized by conditions of the parathyroid glands, pancreas, and pituitary gland. Patients with MEN2 commonly experience a form of thyroid cancer and **adrenal tumors**.

MEN1

Enlarged and overactive parathyroid glands, a condition called hyperparathyroidism, is present in 90% to 97% of MEN1 gene carriers and is usually the first condition to develop. The four parathyroid glands are located in the neck region, with a pair of the glands on either side of the thyroid. They produce parathyroid hormone, which regulates calcium and phosphorus levels. Hyperparathyroidism leads to elevated levels of the hormone, resulting in high blood calcium levels (**hypercalcemia**), which can cause kidney stones and weakened bones. All four parathyroid glands tend to develop tumors, but most tumors are benign and **parathyroid cancer** is rare. Hyperparathyroidism may be present during the teenage years, but most individuals are affected by age 40.



The human endocrine system: A. Hypothalamus. B. Pineal. C. Pituitary. D. Parathyroid. E. Thymus. F. Thyroid. G. Adrenals. H. Pancreas. I. Ovaries (female). J. Testes (male). *(Illustration by Electronic Illustrators Group.)*

Pancreatic tumors occur in 40% to 75% of individuals with the MEN1 gene. The pancreas, which sits behind the stomach, has two parts, an endocrine part and an exocrine part. Tumors in MEN1 occur only in the endocrine pancreas. Among the hormones secreted are ones that lower and raise blood sugar levels—insulin and glucagons—and the hormone gastrin, which is secreted into the stomach to aid in digestion. Thirty to 35% of pancreatic tumors are malignant, and they are the tumors most likely to cause cancer in MEN1 patients. Gastrin-produc-

Association of multiple endocrine neoplasias with other conditions

Form	Associated diseases/conditions
MEN 1 (Wermer's syndrome)	Parathyroid hyperplasia Pancreatic islet cell carcinomas, Pituitary hyperplasia Thymus, adrenal, carcinoid tumors (less common)
MEN 2A (Sipple syndrome)	Medullary thyroid carcinoma, Pheochromocytoma Parathyroid hyperplasia
MEN 2B	Medullary thyroid carcinoma, Pheochromocytoma Parathyroid hyperplasia Swollen lips Tumors of mucous membranes (eyes, mouth, tongue, nasal cavities) Enlarged colon Skeletal problems such as spinal curving
Familial medullary thyroid carcinoma	Medullary thyroid carcinoma

ing tumors (gastrinomas) are the most common tumors that form, representing about 50% of the MEN1 pancreatic tumors. Other tumors that form are insulin-producing tumors (insulinomas), representing 25% to 30%, and glucagon-producing tumors (glucagonomas), representing 5% to 10%.

Gastrinomas can cause recurring upper gastrointestinal ulcers, a condition called **Zollinger-Ellison syndrome**. About half of MEN1 patients with a pancreatic condition develop this syndrome. Insulinomas raise the insulin level in the blood and can lead to hypoglycemia, or low blood sugar (glucose), resulting in glucose levels that are too low to fuel the body's activity. Glucagonomas can cause high blood sugar levels, or hyperglycemia.

Pituitary tumors are the third most common condition in MEN1, occurring in about 50% of MEN1 patients. Fewer than 5% of these tumors are malignant. The pituitary gland, located at the base of the brain, secretes many hormones that regulate the function of other endocrine glands. The most common tumors forming in MEN1 patients are prolactin-producing tumors (prolactinomas) and growth hormone–secreting tumors, which lead to a condition known as acromegaly.

MEN2

Patients with MEN2A and MEN2B experience two main symptoms, medullary thyroid cancer (MTC) and a medullary adrenal tumor known as **pheochromocytoma**. Additional symptoms distinguish the two forms of MEN2. Twenty percent of MEN2A patients develop parathyroid tumors, which have not been reported for MEN2B. As in MEN1, parathyroid tumors in MEN2A affect all four glands and are usually benign. MEN2B is further characterized by the occurrence of benign tumors of the tongue, nasal cavities, and other facial surfaces (mucosal neuromas) and by a condition known as marfanoid habitus. Marfanoid habitus features a characteristic appearance resulting from severe wasting of the proximal muscles. A distinct facial appearance—an elongated face with a thick forehead, wide-eyed look, and broad nose—is often noted at birth. Gastrointestinal, skeletal, and pigmentation abnormalities may also occur. Mucosal neuromas occur in all MEN2B patients, and marfanoid habitus occurs in 65%. About 5% of MEN2 cases are MEN2B.

Ninety-five percent of MEN2A patients and 90% of MEN2B patients develop medullary thyroid **carcinoma** (MTC). Medullary thyroid carcinoma forms from the C-cells of the thyroid. C-cells make the hormone **calcitonin**, which is involved in regulating the calcium levels in the blood and calcium absorption by the bones. The thyroid, which is located in the front of the neck between the Adam's apple and the collarbone, also secretes hormones that are essential for the regulation of body temperature, heart rate, and metabolism.

Medullary thyroid carcinoma causes high blood levels of calcitonin. In MEN2B, MTC develops earlier and is more aggressive than in MEN2A. It has been described in MEN2B patients younger than one year, whereas in MEN2A patients it is likely to occur between the ages of 20 and 40.

Pheochromocytoma is found in 50% of MEN2A patients and 45% of MEN2B patients. A tumor of the medulla portion of the adrenal gland, it is usually a slow-growing and benign adrenal tumor. The two flat adrenal glands, one situated above each kidney, secrete the hormones epinephrine and norepinephrine to increase heart rate and blood pressure, along with other effects. Excessive secretion of these adrenal hormones can cause life-threatening hypertension and cardiac arrhythmia. Tumors form on both adrenal glands in 50% of MEN2 patients diagnosed with a pheochromocytoma. Tumor malignancy is very rare.

Demographics

MEN syndromes are rare. MEN1 occurs in about three to twenty persons out of 100,000, and MEN2 occurs in about three out of 100,000 people. Both MEN1 and MEN2 show no geographic, racial, or ethnic trend, and men and women have an equal chance of acquiring the MEN syndromes.

Ninety-eight percent of MEN1 gene carriers will develop varying combinations of tumors by age 30, but cancer has not been reported in patients younger than 18.

Seventy percent of MEN2A gene carriers will have symptoms by age 70, with most diagnoses occurring between the ages of 30 and 50. MEN2B can occur before one year of age, but most symptoms appear anytime between the ages of 20 and 70.

Causes and symptoms

MEN1

MEN1 is caused by mutations of the MEN1 gene. The MEN1 gene encodes for a previously unknown protein named menin. The role of menin in tumor formation in endocrine glands is not known. But the MEN1 gene is thought to be one of a group of genes known as a tumor suppressor gene. A patient who inherits one defective copy of a tumor suppressor gene from either parent has a strong predisposition to the disease because of the high probability of incurring a second mutation in at least one dividing cell. That cell no longer possesses even one normal copy of the gene. When both copies are defective, tumor suppression fails and tumors develop.

As of 2001, a number of different mutations have been discovered in the MEN1 gene, but people having the same mutation do not always develop the same endocrine conditions. Members within a single family can show different sets of conditions. The symptoms of MEN1 depend on the endocrine condition present:

- Hyperparathyroidism: weakness, **fatigue**, constipation, kidney stones, loss of appetite (anorexia), and bone and joint pain.
- Gastrinoma: peptic ulcers of the stomach and small intestine, **diarrhea**, and **weight loss**.
- Insulinoma: hypoglycemia characterized by weakness, shakiness, fast heartbeat, and difficulty concentrating.
- Glucagonoma: hyperglycemia characterized by inflammation of the tongue or stomach, **anemia**, weight loss, diarrhea, and blood clots.
- Prolactinoma: secretion of milk in women who are not nursing, headaches, sweating, fatigue, weight gain, fertility problems in men and women, and visual problems.
- Acromegaly: enlarged hands and feet, enlarged face, thickened oily skin, fatigue, sweating, bone and joint pain, weight gain, and high blood sugar.

MEN2

Both types of MEN2 are caused by mutations of the RET gene. The RET gene is a cancer-causing gene, or an oncogene. A number of different mutations lead to MEN2A, but only one specific genetic alteration leads to MEN2B.

Unlike for MEN1, the likelihood of developing different conditions in MEN2A is associated with specific mutations of the RET gene. Family history can indicate which conditions current family members are likely to develop. The symptoms of MEN2 are those that accompany hyperparathyroidism, MTC, and pheochromocytoma:

- Medullary thyroid cancer: enlargement of thyroid or neck swelling; lumps or nodules in the neck, pain in the neck region going to the ears, persistent cough unrelated to a cold, cough with bleeding, diarrhea or constipation, hoarseness, and difficulty swallowing or breathing.
- Pheochromocytoma: headaches, sweating, chest pains, feelings of anxiety.

The conditions of MEN2B patients show a variety of additional symptoms, including the occurrence of mucosal neuromas and marfanoid habitus, which is characterized by an elongated face, a thick forehead, and poor muscle development.

Diagnosis

The occurrence of one endocrine condition does not immediately lead to a suspicion of MEN syndromes. Diagnoses is based on the occurrence of one or more endocrine conditions and a family history of MEN1 or MEN2.

Since 1994, **genetic testing** using DNA technology has been available for both MEN1 and MEN2. The identification of the MEN1 gene in 1997 has made genetic screening for this gene more accurate.

A blood sample is usually analyzed for DNA testing, although other tissue can be used. The sample is sent to a laboratory that specializes in DNA diagnosis. There a geneticist will perform several tests on the DNA collected from the cells in blood sample. The exact tests performed will depend on whether MEN1 or MEN2 is suspected. Because different regions of the RET gene are associated with different endocrine conditions in MEN2A, several regions of the gene are examined. A positive result means the defective gene is present, and a negative result means the defective gene is not present.

The test results for the RET gene mutations are more reliable than for the MEN1 gene because detection techniques for identifying MEN1 are still being developed. A clinical diagnosis of MEN2 is confirmed with genetic testing 90–95% of the time. Even when a genetic test is negative, family medical records will be carefully reviewed to confirm the presence of MEN2, and periodic screening of related conditions will likely continue until age 30 or 40. The time required to obtain the test results for MEN2 is about 2–4 weeks, but MEN1 results will

likely take longer because there are fewer diagnostic labs set up for MEN1 analysis.

Those considered at risk for MEN1 or MEN2 based on genetic tests or family history are offered preventative surgery, regular screening for associated endocrine conditions, or a combination of these treatment options. Conditions are screened following the accepted procedure for each condition. Diagnosis is based on clinical features and on testing for elevated hormone levels.

MEN1

Hyperparathyroidism is diagnosed when high levels of calcium and intact parathyroid hormone are measured in a blood sample. Normal values of calcium for adults is 4.4–5.3 mg/dl (milligrams per deciliter), and normal values of parathyroid hormone are 10–55 pg/ml (picograms per milliliter). Prior to the parathyroid test, no food should be eaten for at least six hours. An **x ray** of bones may be taken and then examined by a radiologist for signs of low bone density. An x ray of the abdominal region can reveal kidney stones. Patients should be screened yearly.

Diagnosis of a gastrinoma follows established procedures and includes measuring the levels of gastrin in the blood and the level of stomach gastic acid production. Hypoglycemia associated with insulinomas is diagnosed by measuring blood glucose levels. This test may be administered while a patient is experiencing symptoms related to low insulin levels or during a supervised period of fasting. Depending on the type of test given, no food should be eaten from 6–12 hours prior to the test. Normal glucose levels range between 64–128 mg/dl. Blood glucagon levels above the normal range of 50–100 pg/ml can indicate hyperglycemia, which is associated with glucagonomas. Large pancreatic tumors are identified using **computed tomography** (CT scans) or radionuclide imaging, but **ultrasonography** conducted during surgery is the best method for detecting small tumors. There is no accepted system for staging the pancreatic tumors associated with MEN1.

Prolactinomas, the pituitary tumors most often associated with MEN1, are diagnosed when prolactin levels are greater than 20 ng/l (nanograms per liter). A tumor is identified using **magnetic resonance imaging** (MRI). Tumors secreting excess growth hormone are diagnosed when hormone levels are above the upper normal range of 3 ng/l and from observable changes in physical appearance.

MEN2

Medullary thyroid carcinoma is diagnosed by measuring calcitonin levels in blood and urine samples and from a **biopsy** of any thyroid nodules. Levels of calcitonin above 50 pg/ml can indicate the presence of MTC. Patients showing normal calcitonin levels may require a different test, in which calcitonin is measured at regular intervals after an injection of pentagastrin, a synthetic hormone.

Fine needle aspiration is the biopsy procedure used to diagnose MTC and other forms of thyroid cancer. A sample of cells is removed from a nodule, and the cells are then examined under a microscope by a pathologist to determine if cancer cells are present. MTC has four stages, based on the size of the tumor and where the cancer has spread. **Tumor staging** follows the system established for other forms of thyroid cancer.

A high level of epinephrine relative to norepinephrine indicates a pheochromocytoma on one or both adrenal glands. A CT scan, an MRI, or radionuclide imaging will be performed to locate the tumor.

Diagnosis of hyperparathyroidism in MEN2A patients is identical to its diagnosis for MEN1 patients, but with screening recommended every two to three years.

Treatment team

Conditions of MEN syndromes are first diagnosed by a pathologist who interprets blood and urine samples collected at a doctor's office or a clinic. Depending on the specific condition, a doctor specializing in conditions of the endocrine gland (an endocrinologist) may be consulted. When MEN syndromes are suspected, a genetic counselor will help prepare a patient for the genetic testing procedures and results. A geneticist will perform and interpret genetic tests. Since MEN syndromes often require surgery, the surgical team will likely consist of a surgeon experienced in operating on endocrine glands.

Clinical staging, treatments, and prognosis

No comprehensive treatment is available for genetic disorders such as MEN, but the symptoms of many conditions are treatable. Surgical removal of tumors is the recommended treatment for most conditions, and most MEN patients will require more than one endocrine gland surgery during a lifetime.

An important distinction between an endocrine condition in MEN patients and the same condition in patients not diagnosed with MEN is that endocrine tumors for MEN patients are likely to arise in many locations of a single gland or on multiple glands. Treatment options that work for patients with a single endocrine condition may not be effective in MEN patients. Surgery is often more extensive for MEN patients.

Genetic testing can exclude family members who do not have mutations of the RET or MEN1 gene. The advantage of testing is the early treatment and improved outcomes for those who carry the defective gene and relief from unnecessary anxiety and clinical testing for those not having the defective gene.

MEN1

A common approach to treating MEN1 is with regular screening. Surgical procedures may be delayed until a patient has developed clinical symptoms caused by excess hormone or an easily identifiable tumor.

There are two surgical options for MEN1 patients showing multiple symptoms of hyperparathyroidism or for patients having high blood calcium levels (hypercalcemia), even when no symptoms of the condition are present. All parathyroid tissue is identified and removed and parathyroid tissue is implanted in the forearm, or the surgeon removes three parathyroids and one half of the fourth. After surgery, blood calcium levels are regularly tested to ensure that the remaining parathyroid tissue has not enlarged and caused the condition to return. If hyperparathyroidism recurs, a portion of the remaining tissue is removed until calcium levels return to normal or all the remaining tissue is removed. For MEN1 patients, recurrence is likely within 15 years of the first surgery. Patients with no parathyroid tissue must take daily calcium and vitamin D supplements to prevent hypercalcemia.

There are two views on the best screening strategy for pancreatic tumors in MEN1 patients. One approach is yearly screening, particularly for gastrinomas. This strategy emphasizes the earliest possible detection and surgical removal of tumors. The other approach is screening every 2–3 years, with the reasoning that although tumors are detected at a later stage, they can be better managed with drugs and, if necessary, with surgery.

Surgical removal of insulinomas and glucagonomas, as well as of other less commonly occurring pancreatic tumors in MEN1 patients, is generally the recommended treatment because these tumors are difficult to treat with medication.

The best treatment option for gastrinomas is complex because in MEN1 patients there can be multiple gastrinomas of varying sizes on the pancreas and upper portion of the small intestine (duodenum), and they have a tendency to recur. Most doctors support the use of medication to control the condition and do not recommend surgical intervention. Common treatment of symptoms is the use of drugs that block acid production, called acid pump inhibitors. Others recommend surgery that includes removal of the duodenum and a section of the pancreas and cutting nerves to the section of the stomach involved in acid secretion. Surgery is supported as a way to reduce the risk for **metastasis**. In some cases, gastrin levels and gastric acid levels returned to normal, and MEN1 patients experienced no symptoms after the surgery. A treatment no longer recommended is removal of the entire stomach. Malignant gastrinomas cause death in 10% to 20% of MEN1 patients with this condition, and 30% to 50% will eventually spread to the liver.

Treatment of pituitary tumors in MEN1 patients rarely involves surgery. For prolactinomas, medications are effective in returning prolactin levels to normal and preventing tumor growth.

MEN2

Medullary thyroid carcinoma is the primary concern for those testing positive for the RET gene mutations. Since genetic testing became available for MEN2, two approaches have emerged to manage this cancer. Some recommend removing the entire thyroid gland (thyroidectomy) before any symptoms occur, although doctors disagree at what age to perform this surgery. This strategy emerged owing to a number of cases in which thyroids removed from identified MEN2 patients showing no clinical signs of MTC were found to be cancerous. Preventative thyroid surgery is offered to those with RET gene mutations beginning at age 5. Some recommend surgery after age 10, unless calcitonin tests are positive earlier. They contend that surgery before age 10 may increase the chance of damaging the larynx or the parathyroids.

The second approach is yearly blood calcitonin testing beginning in early childhood. A thyroidectomy is performed after the first abnormal calcitonin test. There is only a 10% chance of recurrence 15–20 years after surgery for those identified using this method. The advantage of this method is to delay surgery until it is necessary. The disadvantages are the cost and discomfort of yearly testing. Also, the first detection of elevated levels of calcitonin in the blood may occur after the cancer has already reached an advanced stage.

A thyroidectomy is the standard treatment for all stages of MTC. If MTC is diagnosed in an advanced stage, the spread of the cancer may have already occurred. Metastasis is very serious in MTC because **chemotherapy** and **radiation therapy** are not effective in controlling metastasis. Further tests are likely to include a CT scan and an MRI.

All MTC patients must take thyroid hormone medication for the rest of their lives in order to maintain normal body functions. Follow-up treatment to assure that the cancer has not recurred includes monitoring the lev-

els of calcitonin in the blood. The survival rate 10 years after the initial diagnosis is 46%. If the cancer is detected using genetic screening before the patient shows signs of having the disease, surgical removal of the thyroid gland can cure MTC.

Pheochromocytoma may occur after the MTC diagnosis by as much as 20 years. Pheochromocytoma in MEN2 can be cured by surgical removal of the affected adrenal gland. If a pheochromocytoma occurs on only one gland, there is some debate on whether to remove both adrenal glands or only the affected gland. Fifty percent of MEN2 patients who underwent removal of one adrenal gland developed a pheochromocytoma in the other gland within 10 years. Because malignancy is rare, most doctors recommend removing the affected glands first and then monitoring hormone levels to see if a second tumor occurs. If both glands are removed, hormone replacement therapy is required.

Alternative and complementary therapies

There are no alternative treatments specifically targeted for people with MEN syndromes, although cow and shark cartilage treatments are being investigated as a way to decrease tumor growth in some cancers. These treatments are administered orally, by injection, or as an enema, but studies of the effectiveness of this treatment for humans are inconclusive.

Coping with cancer treatment

The surgery that most MEN syndromes patients will face can cause anxiety and fear. Patients should discuss their concerns about an operation with their personal physician, the surgeon, nurses, and other medical personnel. Getting specific answers to questions can provide a clear idea of what to expect immediately after the surgery as well as any long-term changes in quality of life.

Clinical trials

Clinical studies of MEN syndromes focus on understanding the genes involved in the inheritance of MEN1 and MEN2 and on the unique treatment needs for the endocrine gland conditions occurring in MEN patients. One ongoing study investigates new imaging techniques for locating pheochromocytomas, particularly in MEN2 patients. Contact information:

National Institute of Child Health and Human Development (NICHD), 9000 Rockville Pike, Bethseda, MD 20892. (800) 411-1222

A second clinical trial is a genetic-analysis study of known and suspected individuals with MEN1. Participants are offered genetic counseling with an option for involvement in research designed to improve genetic counseling services. Contact information:

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 9000 Rockville Pike, Bethseda, MD 20892. (800) 411-1222

KEY TERMS

Endocrine—A term used to describe the glands that produce hormones in the body.

Exocrine—A term used to describe organs that secrete substances outward through a duct.

Hyperplasia—An overgrowth of normal cells within an organ or tissue.

Medullary thyroid cancer (MTC)—A slow-growing tumor of which about 20% are associated with MEN2.

Neoplasm—An abnormal formation of tissue; for example, a tumor.

Oncogene—A gene with a mutation that causes cell growth and division, leading to the formation of cancerous tumors.

Pheochromocytoma—A tumor of the medullary of the adrenal gland.

RET (REarranged during Transfection) gene—Located on chromosome 10q11.2, mutations in this gene are associated with two very different disorders, the multiple endocrine neoplasia (MEN) syndromes and Hirschsprung disease.

Tumor suppressor gene—A type of gene that instructs cells on the appropriate time to die. A mutation can turn off the gene, resulting in cell growth and tumor formation.

Prevention

There is no preventive measure to block the occurrence of the genetic mutations that cause MEN syndromes. Medullary thyroid carcinoma, one of the most serious conditions of MEN2, can be prevented by thyroidectomy.

Special concerns

It is important to seek professional genetic counseling before proceeding with genetic testing, particularly for children. Adults may have to make treatment decisions for children.

Genetic tests are often expensive. Whether or not **health insurance** will cover the costs of counseling and

QUESTIONS TO ASK THE DOCTOR

- Are the tumors associated with this condition cancerous?
- Can one endocrine tumor spread to other endocrine glands?
- What are the long-lasting effects of this disorder?
- What are the long-lasting effects of treatment?
- After treatment, what are the chances that a condition will recur?
- Are there alternative treatments to surgery?
- Will I need to take hormone supplements, if so, for how long?
- Will this disorder affect my ability to have children?
- What is the current status of predictive gene testing?
- Who in my family should be tested for this disorder?

testing will depend on individual policies. Some insurance companies cover the costs only when a patient shows symptoms of a condition. Genetic tests raise issues of privacy. Most states in the United States have legislation that restricts the use of genetic test results by insurance companies and employers.

See also Cancer genetics; Familial cancer syndromes; Pancreatic cancer, endocrine; Thyroid cancer.

Resources

PERIODICALS

Hoff, A. O., G. J. Cote, and R. F. Gagel. "Multiple Endocrine Neoplasias." *Annual Review of Physiology* 62 (2000): 377–411.

Noll, Walter W. "Utility of RET Mutation Analysis in Multiple Endocrine Neoplasia Type 2." *Archives of Pathology and Laboratory Medicine* 123 (1999): 1047–9.

ORGANIZATIONS

Canadian MEN Society. P.O. Box 100, Meola, SK, Canada SOM 1XO. (306) 892-2080.

The Genetic Alliance (formerly the Alliance of Genetic Support Groups). 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2304. (202) 966-5557, (800) 336-GENE.

OTHER

Labs Performing MEN Testing. <http://endocrine.mdacc.tmc.edu>.

G. Victor Leipzig
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Multiple myeloma

Definition

Multiple myeloma is a cancer in which antibody-producing plasma cells grow in an uncontrolled and invasive (malignant) manner.

Description

Multiple myeloma, also known as plasma cell myeloma, is the second-most common cancer of the blood. It is the most common type of plasma cell neoplasm. Multiple myeloma accounts for approximately 1% of all cancers and 2% of all deaths from cancer. Multiple myeloma is a disease in which malignant plasma cells spread through the bone marrow and hard outer portions of the large bones of the body. These myeloma cells may form tumors called plasmacytomas. Eventually, multiple soft spots or holes, called osteolytic lesions, form in the bones.

Bone marrow is the spongy tissue within the bones. The breastbone, spine, ribs, skull, pelvic bones, and the long bone of the thigh all are particularly rich in marrow. Bone marrow is a very active tissue that is responsible for producing the cells that circulate in the blood. These include the red blood cells that carry oxygen, the white blood cells that develop into immune system cells, and platelets, which cause blood to clot.

Plasma cells and immunoglobulins

Plasma cells develop from B lymphocytes or B cells, a type of white blood cell. B cells, like all blood cells, develop from unspecialized stem cells in the bone marrow. Each B cell carries a specific antibody that recognizes a specific foreign substance called an antigen. Antibodies are large proteins called immunoglobulins (Igs), which recognize and destroy foreign substances and organisms such as bacteria. When a B cell encounters its antigen, it begins to divide rapidly to form mature plasma cells. These plasma cells are all identical (monoclonal). They produce large amounts of identical antibody that are specific for the antigen.

Malignant plasma cells

Multiple myeloma begins when the genetic material (DNA) is damaged during the development of a stem cell into a B cell in the bone marrow. This causes the cell to develop into an abnormal or malignant plasmablast, a developmentally early form of plasma cell. Plasmablasts produce adhesive molecules that allow them to bond to the inside of the bone marrow. A growth factor, called interleukin-6, promotes uncontrolled growth of these myeloma cells in the bone marrow and prevents their natural death. Whereas normal bone marrow contains less than 5% plasma cells, bone marrow of an individual with multiple myeloma contains over 10% plasma cells.

In most cases of multiple myeloma, the malignant plasma cells all make an identical Ig. Igs are made up of four protein chains that are bonded together. Two of the chains are light and two are heavy. There are five classes of heavy chains, corresponding to five types of Igs with different immune system functions. The Igs from myeloma cells are nonfunctional and are called paraproteins. All of the paraproteins from any one individual are monoclonal (identical) because the myeloma cells are identical clones of a single plasma cell. Thus, the paraprotein is a monoclonal protein or M-protein. The M-proteins crowd out the functional Igs and other components of the immune system. They also cause functional antibodies, which are produced by normal plasma cells, to rapidly break down. Thus, multiple myeloma depresses the immune system.

In about 75% of multiple myeloma cases, the malignant plasma cells also produce monoclonal light chains, or incomplete Igs. These are called Bence-Jones proteins and are secreted in the urine. Approximately 1% of multiple myelomas are called nonsecretors because they do not produce any abnormal Ig.

Osteolytic lesions

About 70% of individuals with multiple myeloma have soft spots or lesions in their bones. These lesions can vary from quite small to grapefruit-size. In part, these lesions occur because the malignant plasma cells rapidly outgrow the normal bone-forming cells. In addition, malignant myeloma cells produce factors that affect cells called osteoclasts. These are the cells that normally destroy old bone, so that new bone can be produced by cells called osteoblasts. The myeloma cell factors increase both the activation and the growth of osteoclasts. As the osteoclasts multiply and migrate, they destroy healthy bone and create lesions. Osteoporosis, or widespread bone weakness, may develop.

Demographics

There are more than 40,000 multiple myeloma patients in the United States. The American Cancer Society predicts an additional 14,400 new cases in 2001. About 11,200 Americans will die of the disease in 2001. Multiple myeloma is one of the leading causes of cancer deaths among African-Americans.

In Western industrialized countries, approximately four people in 100,000 develop multiple myeloma. The incidence of multiple myeloma among African Americans is 9.5 per 100,000, about twice that of Caucasians. Asians have a much lower incidence of the disease. In China, for example, the incidence of multiple myeloma is only one in 100,000. The offspring and siblings of individuals with multiple myeloma are at a slightly increased risk for the disease.

At diagnosis, the average age of a multiple myeloma patient is 68 to 70. Although the average age at onset is decreasing, most multiple myelomas still occur in people over 40. This cancer is somewhat more prevalent in men than in women.

Causes and symptoms

Associations

The cause of multiple myeloma has not been determined. However, a number of possible associations have been identified:

- decreased immune system function; the immune systems of older individuals may be less efficient at detecting and destroying cancer cells
- genetic (hereditary) factors, suggested by the increased incidence in some ethnic groups and among family members
- occupational factors, suggested by the increased incidence among agricultural, petroleum, wood, and leather workers, and cosmetologists
- long-term exposure to herbicides, pesticides, petroleum products, heavy metals, plastics, and dusts such as asbestos
- radiation exposure, as among Japanese atomic bomb survivors, nuclear weapons workers, and medical personnel such as radiologists
- Kaposi's sarcoma-associated herpes virus (also called human herpes virus-8 or HHV-8), found in the blood and bone marrow cells of many multiple myeloma patients

Early symptoms

The accumulation of malignant plasma cells can result in tiny cracks or fractures in bones. Malignant

plasma cells in the bone marrow can suppress the formation of red and white blood cells and platelets. About 80% of individuals with multiple myeloma are anemic due to low red blood cell formation. Low white blood cell formation results in increased susceptibility to infection, since new, functional antibodies are not produced. In addition, normal circulating antibodies are rapidly destroyed. Low platelet formation can result in poor blood clotting. It is rare, however, that insufficient white blood cell and platelet formations are presenting signs of multiple myeloma.

These factors cause the early symptoms of multiple myeloma:

- pain in the lower back or ribs
- fatigue and paleness due to **anemia** (low red blood cell count)
- frequent and recurring infections, including bacterial **pneumonia**, urinary-tract and kidney infections, and shingles (herpes zoster)
- bleeding

Bone destruction

Bone pain, particularly in the backbone, hips, and skull, is often the first symptom of multiple myeloma. As malignant plasma cells increase in the bone marrow, replacing normal marrow, they exert pressure on the bone. As overly active osteoclasts (large cells responsible for the breakdown of bone) remove bone tissue, the bone becomes soft. Fracture and **spinal cord compression** may occur.

Plasmacytomas (malignant tumors of plasma cells) may weaken bones, causing fractures. Fractured bones or weak or collapsed spinal bones, in turn, may place unusual pressure on nearby nerves, resulting in nerve pain, burning, or numbness and muscle weakness. Proteins produced by myeloma cells also may damage nerves.

Calcium from the destroyed bone enters the blood and urine, causing **hypercalcemia**, a medical condition in which abnormally high concentrations of calcium compounds exist in the bloodstream. High calcium affects nerve cell and kidney function. The symptoms of hypercalcemia include:

- weakness and fatigue
- depression
- mental confusion
- constipation
- increased thirst
- increased urination
- nausea and vomiting
- kidney pain
- kidney failure

Hypercalcemia affects about one-third of multiple myeloma patients.

Serum proteins

The accumulation of M-proteins in the serum (the liquid portion of the blood) may cause additional complications, such as hyperviscosity syndrome, or thickening of the blood (though rare in multiple myeloma patients). Symptoms of hyperviscosity include:

- fatigue
- headaches
- shortness of breath
- mental confusion
- chest pain
- kidney damage and failure
- vision problems
- Raynaud's disease (Raynaud's phenomenon, can affect any part of the body, but particularly the fingers, toes, nose, and ears.)

Cryoglobulinemia occurs when the protein in the blood forms particles under cold conditions. These particles can block small blood vessels and cause pain and numbness in the toes, fingers, and other extremities during cold weather.

Amyloidosis is a rare complication of multiple myeloma. It usually occurs in individuals whose plasma cells produce only Ig light chains. These Bence-Jones proteins combine with other serum proteins to form amyloid protein. This starchy substance can invade tissues, organs, and blood vessels. In particular, amyloid proteins can accumulate in the kidneys, where they block the tiny tubules that are the kidney's filtering system. Indicators of amyloidosis include:

- carpal tunnel syndrome
- kidney failure
- liver failure
- heart failure

Diagnosis

Blood and urine tests

Often, the original diagnosis of multiple myeloma is made from routine blood tests that are performed for other reasons. Blood tests may indicate:

- anemia
- abnormal red blood cells
- high serum protein levels
- low levels of normal antibody
- high calcium levels
- high blood urea nitrogen (BUN) levels
- high creatinine levels

Urea and creatinine normally are excreted in the urine. High levels of urea and creatinine in the blood indicate that the kidneys are not functioning properly to eliminate these substances.

Protein electrophoresis is a laboratory technique that uses an electrical current to separate the different proteins in the blood and urine on the basis of size and charge. Since all of the multiple myeloma M-proteins in the blood and urine are identical, electrophoresis of blood and urine from a patient with multiple myeloma shows a large M-protein spike, corresponding to the high concentration of monoclonal Ig. Electrophoresis of the urine also can detect Bence-Jones proteins.

Bones

A bone marrow aspiration utilizes a very thin, long needle to remove a sample of marrow from the hip bone. Alternatively, a bone marrow **biopsy** with a larger needle removes solid marrow tissue. The marrow is examined under the microscope for plasma cells and tumors. If 10% to 30% of the cells are plasma cells, multiple myeloma is the usual diagnosis.

X rays are used to detect osteoporosis, osteolytic lesions, and fractures. Computed tomography (CAT or CT) scans can detect lesions in both bone and soft tissue. **Magnetic resonance imaging** (MRI) may give a more detailed image of a certain bone or a region of the body.

Treatment team

After the initial diagnosis, the treatment team for multiple myeloma may include a hematologist (a specialist in diseases of the blood) and an oncologist or cancer specialist. If radiation is used in treatment, a radiation oncologist may join the team. The treatment of multiple myeloma involves complex decisions, and obtaining second opinions from additional specialists may be important.

Clinical staging, treatments, and prognosis

Related disorders

Monoclonal gammopathy of undetermined significance (MGUS) is a common condition in which a monoclonal Ig is detectable. However, there are no tumors or other symptoms of multiple myeloma. MGUS occurs in about 1% of the general population and in about 3% of those over age 70. Over a period of years, about 16% to 20% of those with MGUS will develop multiple myeloma or a related cancer called malignant **lymphoma**.

Occasionally, only a single plasmacytoma develops, either in the bone marrow (isolated plasmacytoma of the bone) or other tissues or organs (extramedullary plasmacytoma). Some individuals with solitary plasmacytoma may develop multiple myeloma.

Clinical stages

The Durie-Salmon system is used to stage multiple myeloma. Stage I multiple myeloma requires all of the following (1 gram = approx. 0.02 pints, 1 deciliter = approx. 0.33 fluid ounces):

- hemoglobin (the oxygen-transporting molecule of red blood cells) above 10 grams/deciliter (g/dl)
- serum calcium below 12 mg/dl
- normal bone structure or only isolated plasmacytoma
- low M-protein, based on established guideline levels of Ig protein chains

Approximately 5% of multiple myeloma cases are not progressing at diagnosis, and may not progress for months or years. This is called smoldering myeloma. These patients have stage I blood chemistry but no symptoms.

Stage II multiple myeloma fits neither stage I nor stage III. Stage III multiple myeloma meets one or more the following criteria:

- hemoglobin below 8.5 g/dl
- serum calcium above 12 mg/dl
- advanced bone lesions
- high M-protein

Each stage is subclassified as A or B, based on serum creatinine indicators of normal or abnormal kidney function. Most patients have stage III multiple myeloma at diagnosis.

Prognostic indicators

Prognostic indicators for multiple myeloma may be used instead of, or in addition to, the staging system described above. Prognostic indicators are laboratory tests that help to define the stage of the disease at diagnosis, and its progression during treatment. These indicators are:

- plasmablastic multiple myeloma (presence of plasmablasts, the precursor malignant plasma cells)

- plasma cell labeling index (the percentage of plasma cells that are actively dividing)
- beta 2-microglobulin, a protein secreted by B cells that correlates with the myeloma cell mass (also indicates kidney damage)

Treatment

Since multiple myeloma often progresses slowly, and since the treatments can be toxic, the disease may not be treated until M-protein levels in the blood are quite high. In particular, MGUS and smoldering myeloma may be followed closely but not treated. Solitary plasmacytomas are treated with radiation and/or surgery and followed closely with examinations and laboratory tests.

CHEMOTHERAPY **Chemotherapy**, or treatment with anti-cancer drugs, is used for multiple myeloma. MP, a combination of the drugs **melphalan** and prednisone, is the standard treatment. Usually, the drugs are taken by mouth every 3 to 4 weeks for 6 to 9 months or longer, until the M-protein levels in the blood stop decreasing. MP usually results in a 50% reduction in M-protein.

Dexamethasone, a corticosteroid, sometimes is used to treat the elderly or those in poor health. It can drop the M-protein levels by 40% in untreated individuals and by 20% to 40% in patients who have not responded to previous treatment. Other chemotherapy drugs, including **cyclophosphamide**, **carmustine**, **doxorubicin**, **vincristine**, and **chlorambucil**, may be used as well.

Multiple myeloma usually recurs within a year after the end of chemotherapy. Although the chemotherapy can be repeated after each recurrence, it is progressively less responsive to treatment.

Side effects of chemotherapy may include:

- anemia
- hair loss (alopecia)
- nausea and vomiting
- diarrhea
- mood swings
- swelling
- acne

These side effects disappear after treatment is discontinued.

OTHER DRUG TREATMENTS **Bisphosphonates** are drugs that inhibit the activity of osteoclasts. These drugs can slow the progression of bone disease, reduce pain, and help prevent bone fractures. Different types of bisphosphonates inhibit osteoclasts in different ways. They also reduce the production of interleukin-6 by bone marrow cells. Laboratory studies suggest that bisphosphonates may kill or inhibit the growth of multiple myeloma cells. Pamidronate is the most common bisphosphonate for treating multiple myeloma.

Portion of spine from patient with multiple myeloma. In this disease, malignant plasma cells spread through the bone marrow and hard outer portions of the body's large bones. As malignant plasma cells increase in the bone marrow, replacing normal marrow, they exert pressure on the bone. Bones become soft and may fracture; spinal bones may collapse. *(Custom Medical Stock Photo. Reproduced by permission.)*

The drug **thalidomide** appears to have several anti-myeloma activities. Thalidomide affects the immune system in various ways and it appears to inhibit myeloma cells, both directly and indirectly. It also inhibits the growth of new blood vessels that are needed by tumors. However, if thalidomide is taken during pregnancy, it can cause severe birth defects or death of the fetus.

KEY TERMS

Amyloidosis—A complication of multiple myeloma in which amyloid protein accumulates in the kidneys and other organs, tissues, and blood vessels.

Anemia—Any condition in which the red blood cell count is below normal.

Antibody—Immunoglobulin produced by immune system cells that recognizes and binds to a specific foreign substance (antigen).

Antigen—Foreign substance that is recognized by a specific antibody.

B cell (B lymphocyte)—Type of white blood cell that produces antibodies.

Bence-Jones protein—Light chain of an immunoglobulin that is overproduced in multiple myeloma and is excreted in the urine.

Beta 2-microglobulin—Protein produced by B cells; high concentrations in the blood are indicative of multiple myeloma.

Cryoglobulinemia—Condition triggered by low temperatures in which protein in the blood forms particles, blocking blood vessels, leading to pain and numbness of the extremities.

Electrophoresis—Use of an electrical field to separate proteins in a mixture (such as blood or urine), on the basis of the size and electrical charge of the proteins.

Hemoglobin—Protein in red blood cells that carries oxygen.

Hypercalcemia—Abnormally high levels of calcium in the blood.

Hyperviscosity—Thick, viscous blood, caused by the accumulation of large proteins, such as immunoglobulins, in the serum.

Immunoglobulin (Ig)—Antibody; large protein produced by B cells that recognizes and binds to a specific antigen.

M-protein—Monoclonal or myeloma protein; paraprotein; abnormal antibody found in large amounts in the blood and urine of individuals with multiple myeloma.

Malignant—A characteristic of cancer cells that grow uncontrollably and invade other tissues.

Monoclonal—Identical cells or proteins; cells (clones) derived from a single, genetically distinct cell, or proteins produced by these cells.

Monoclonal gammopathy of undetermined significance (MGUS)—Common condition in which M-protein is present, but there are no tumors or other symptoms of disease.

Neoplasm—Tumor made up of cancer cells.

Osteoblast—Bone-forming cell.

Osteoclast—Cell that absorbs bone.

Osteolytic lesion—Soft spot or hole in bone caused by cancer cells.

Osteoporosis—Condition in which the bones become weak and porous, due to loss of calcium and destruction of cells.

Paraprotein—M-protein; abnormal immunoglobulin produced in multiple myeloma.

Plasma cell—Type of white blood cell that produces antibodies; derived from an antigen-specific B cell.

Platelet—Cell that is involved in blood clotting.

Stem cell—Undifferentiated cell that retains the ability to develop into any one of numerous cell types.

The drug **allopurinol** may be used to reduce high blood levels of uric acid that result from kidney dysfunction. Diuretics can improve kidney function. Infections require prompt treatment with **antibiotics**.

BONE AND PERIPHERAL BLOOD STEM CELL TRANSPLANTATION Bone marrow or peripheral blood stem cell transplantations (PBSCT) are used to replace the stem cells of the bone marrow following high-dosage chemotherapy. Chemotherapy destroys the bone marrow stem cells that are necessary to produce new blood cells. In an autologous transplant, the patient's bone marrow stem cells or peripheral blood stem cells (immature bone marrow cells found in the blood) are collected, treated with drugs to kill any myeloma cells, and frozen prior to chemotherapy. Growth factors are used to increase the number of peripheral stem cells prior to collection. A procedure called apheresis is used to collect the peripheral stem cells. Following high-dosage chemotherapy, the stem cells are reinjected into the individual. In an allogeneic transplant, the donor stem cells come from a genetically related individual such as a sibling.

OTHER TREATMENTS Blood transfusions may be required to treat severe anemia.

Plasmapheresis, or plasma exchange transfusion, may be used to thin the blood to treat hyperviscosity syndrome. In this treatment, blood is removed and passed through a machine that separates the plasma, containing the M-protein, from the red and white blood cells and platelets. The blood cells are transfused back into the patient, along with a plasma substitute or donated plasma.

Multiple myeloma may be treated with high-energy x rays directed at a specific region of the body. **Radiation therapy** is used for treating bone pain.

Alternative and complementary therapies

Interferon alpha, an immune-defense protein that is produced by some white blood cells and bone marrow cells, can slow the growth of myeloma cells. It usually is given to patients following chemotherapy, to prolong their remission. However, interferon may have toxic effects in older individuals with multiple myeloma.

Once multiple myeloma is in remission, calcium and vitamin D supplements can improve bone density. It is important not to take these supplements when the myeloma is active. Individuals with multiple myeloma must drink large amounts of fluid to counter the effects of hyperviscous blood.

Prognosis

The prognosis for individuals with MGUS or solitary plasmacytoma is very good. Most do not develop multiple myeloma. However, approximately 15% of all patients with multiple myeloma die within three months of diagnosis. About 60% respond to treatment and live for an average of two and a half to three years following diagnosis. Approximately 23% of patients die of other illnesses associated with advanced age.

The prognosis for a given individual may be based on the prognostic indicators described above. The median survival for those without plasmablasts, and with a low plasma cell labeling index (PCLI) and low beta 2-microglobulin, is 5.5 years. The median survival for patients with plasmablastic multiple myeloma, or with a high PCLI (1% or greater) and high beta 2-microglobulin (4 or higher), is 1.9 and 2.4 years, respectively. Many multiple myeloma patients are missing part or all of chromosome 13. The deletion of this chromosome, along with high beta 2-microglobulin, leads to a poor prognosis.

With treatment, multiple myeloma may go into complete remission. This is defined as:

- M-protein absent from the blood and urine
- myeloma cells not detectable in the bone marrow
- no clinical symptoms
- negative laboratory tests

However, with very sensitive testing, a few myeloma cells are usually detectable and eventually lead to a recurrence of the disease, in the bone or elsewhere in the body.

Coping with cancer treatment

Techniques such as biofeedback, guided imagery, and meditation may be helpful for reducing stress and relieving pain. Pain medication is usually prescribed for multiple myeloma. Back or neck braces may help relieve bone pain. Exercise, if possible, is important for retaining calcium in the bones.

Clinical trials

There are hundreds of ongoing **clinical trials** for the treatment of multiple myeloma. These take place throughout the United States and are sponsored by both government and industry. Clinical trials of treatments for multiple myeloma include:

- thalidomide
- thalidomide-like drugs that affect the immune system in various ways
- skeletal targeted radiotherapy (STP), in which a radioactive element is attached to a drug that binds to bone
- new anti-cancer drugs
- new combinations of drugs
- new chemotherapies in combination with PBSCT
- combinations of PBSCT, interleukin-2, and interferon alpha
- treatments for disease resulting from PBSCT (graft-versus-host disease)
- bone marrow transplantations
- immunotherapies, including **vaccines**, to destroy remaining myeloma cells after high-dosage chemotherapy and PBSCT
- treatments for MGUS

Prevention

There are no clearly established risk factors for multiple myeloma and it is possible that a combination of factors interact to cause the disease. Thus, there is no method for preventing multiple myeloma.

Special concerns

Since there is a high probability that multiple myeloma will recur after treatment, patients are followed

QUESTIONS TO ASK THE DOCTOR

- What stage of multiple myeloma do I have and what does it mean?
- What are my treatment options?
- What are the side effects of treatment?
- Are there clinical trials that may be appropriate for me?
- How long can I expect to survive?
- Is my cancer likely to recur?

carefully. Blood tests, x rays, and other **imaging studies** may be used to check for a recurrence.

See also Bone marrow transplantation; Immunoelectrophoresis; Pheresis; Protein electrophoresis.

Resources

BOOKS

Holland, Jimmie C., and Sheldon Lewis. *The Human Side of Cancer: Living with Hope, Coping with Uncertainty*. New York: HarperCollins, 2000.

ORGANIZATIONS

International Myeloma Foundation. 12650 Riverside Dr., Suite 206, North Hollywood, CA 91607. (800) 452-CURE. (818) 487-7455. <http://www.myeloma.org>. Information and support for patients and families and the scientific and medical communities.

The Leukemia and Lymphoma Society. 600 Third Avenue, New York, NY 10016. (800) 955-4572. (914) 949-5213. <http://www.leukemia-lymphoma.org>. Information, support, and guidance for patients and health care professionals.

Multiple Myeloma Research Foundation. 11 Forest Street, New Canaan, CT 06840. (203) 972-1250. <http://www.multiplemyeloma.org>. Information and research funding.

OTHER

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Margaret Alic, Ph.D.

Muromonab-CD3

Definition

Muromonab-CD3 is a mouse-derived (murine) monoclonal antibody that specifically binds to the CD3 (T3) protein found on the surface of T cells. It is a protein known to be necessary for activation (immune responses) of T cells. Muromonab-CD3 is marketed in the United States under the Orthoklone OKT3 brand name.

Purpose

Muromonab-CD3 is believed to have two effects when it binds to the CD3 protein on the surface of T cells. In the short term the T cells are activated and begin to excrete cytokines—small proteins that boost immune function. In the long term, function of the T cells is eliminated because access to the CD3 protein is blocked and binding by the antibody encourages removal of the cell from the bloodstream by the immune system.

When using muromonab-CD3 to treat cancer, doctors are seeking the short-term effect by boosting the activity of T cells against tumor antigens. In this setting muromonab-CD3 is not administered directly to the patient. Rather, it is used to stimulate white blood cells (lymphocytes) that have been removed from the patient, treated outside the body, then reinfused (infused back into the patient). In the test tube the binding of the antibody to the CD3 protein stimulates the T cells so they can begin the cell-mediated destruction of the tumor cells upon reentry into the patient's bloodstream. Often, the T cells used for this treatment are either preselected to be specific against the proteins found on the tumor surface (tumor antigens) or are genetically engineered

KEY TERMS

Antibody—A protective protein made by the immune system in response to an antigen; also called an immunoglobulin.

Cytokine—A protein produced by cells of the immune system that help boost immune function.

hOKT3—A humanized version of the muromonab-CD3 antibody.

Humanization—Fusing the constant and variable framework region of one or more human immunoglobulins with the binding region of an animal immunoglobulin; done to reduce human reaction against the fusion antibody.

Interleukin-2—A cytokine responsible for the activation of B and T cells of the immune system that induces growth and maturation of those cells.

Monoclonal antibody—Genetically engineered antibodies specific for one antigen.

before reinfusion to express the desired tumor-antigen specific receptors. This is often followed by stimulation of T-cell division using interleukin-2.

Clinical trials using this stimulated lymphocyte treatment are ongoing for **astrocytoma**, oligodendroglioma, nonmetastatic kidney cancer, metastatic **melanoma**, **Kaposi's sarcoma** (a twin study), and advanced epithelial **ovarian cancer**.

Description

In late 1986, Muromonab-CD3 was the first monoclonal antibody approved for use by the FDA as an immunosuppressive drug in kidney transplantation. The use of this drug in transplantation is based on the long-term effect of antibody binding, blocking cellular interaction with the CD3 protein known to be necessary to activate T cells involved in the rejection of transplanted tissue. As of mid-2001, it had not been approved for use as a cancer therapy. However, there were at least five active clinical trials to test its ability to activate lymphocytes outside the body in preparation for reinfusion.

A second use of the muromonab-CD3 antibody to treat cancer required the development of a humanized monoclonal antibody called hOKT3, using the same binding sites as muromonab-CD3. This treatment involves direct administration of the antibody to the patient. The humanized antibody retains the murine sequences at the antibody's two binding sites, but has human sequences in the other areas of the antibody molecule. This allows the monoclonal antibody to be directly administered to the patient without the immune reaction against the mouse antibodies seen when muromonab-CD3 is used. hOKT3 was used in a clinical trial of 24 patients against a wide variety of cancers. Although testing the antibody's function as a therapy was not the main goal of the study, three patients with cancers of the peritoneum cavity (lower abdomen) did see a clinical improvement.

Recommended dosage

To treat cancer, muromonab-CD3 is not administered directly to the patient. However, a similar humanized antibody, hOKT3, has been given to patients during a clinical trial. The most effective dosage in the trial was three doses of 800 micrograms every two weeks in a 10-minute infusion, but further study is necessary to confirm this finding.

Precautions

As the two uses of muromonab-CD3 are still in the clinical trial stage, the exact precautions for this drug (or the humanized version, hOKT3) are not yet known. However, for monoclonal antibody treatment in general, preexisting heart conditions and arrhythmias can make taking this drug more dangerous. Vaccination during the treatment session is also not recommended, given the T-cell depletion that occurs during treatment.

Side effects

During clinical trials the majority of side effects occurred during the first administration of activated T cells or humanized antibody. These side effects included flu-like symptoms, headache, dizziness, and shortness of breath. The humanized antibody also caused edema (collection of fluid) in all three patients who exhibited a clinical benefit from the treatment.

Interactions

Still in the early clinical trial stages in 2001, muromonab-CD3 had not been studied to determine interactions with other drugs.

Michelle Johnson, M.S., J.D.

Myasthenic syndrome of Lambert-Eaton

see **Eaton-Lambert syndrome**

Myasthenia gravis

Description

Myasthenia gravis (MG) is an autoimmune disease that causes muscle weakness. It affects the neuromuscular junction, interrupting the communication between nerve and muscle, and thereby causing weakness. People with MG may have difficulty moving their eyes, walking, speaking clearly, swallowing, and even breathing, depending on the severity and distribution of weakness. Increased weakness with exertion, and improvement with rest, is a characteristic feature of MG.

About 30,000 people in the United States are affected by MG. It can occur at any age, but is most common in women who are in their late teens and early twenties, and in men in their sixties and seventies.

MG has been associated with malignant **thymoma**, a disease in which cancer cells are found in the tissues of the thymus.

Causes

Myasthenia gravis is an autoimmune disease, meaning that it is caused by the body's own immune system. In MG, the immune system attacks a receptor on the surface of muscle cells. This prevents the muscle from receiving the nerve impulses that normally make it respond. MG affects "voluntary" muscles, which are those muscles under conscious control responsible for movement. It does not affect heart muscle or the "smooth" muscle found in the digestive system and other internal organs.

A muscle is stimulated to contract when the nerve cell controlling it releases acetylcholine molecules onto its surface. The acetylcholine lands on a muscle protein called the acetylcholine receptor. This leads to rapid chemical changes in the muscle which cause it to contract. Acetylcholine is then broken down by acetylcholinesterase enzyme, to prevent further stimulation.

In MG, immune cells create antibodies against the acetylcholine receptor. Antibodies are proteins normally involved in fighting infection. When these antibodies attach to the receptor, they prevent it from receiving acetylcholine, decreasing the ability of the muscle to respond to stimulation.

Why the immune system creates these self-reactive "autoantibodies" is unknown, although there are several hypotheses:

- During fetal development, the immune system generates many B cells that can make autoantibodies, but B cells that could harm the body's own tissues are screened out and destroyed before birth. It is possible that the stage is set for MG when some of these cells escape detection.
- Genes controlling other parts of the immune system, called MHC genes, appear to influence how susceptible a person is to developing autoimmune disease.
- Infection may trigger some cases of MG. When activated, the immune system may mistake portions of the acetylcholine receptor for portions of an invading virus, though no candidate virus has yet been identified conclusively.
- About 10% of those with MG also have thymomas, or tumors of the thymus gland. The thymus is a principal organ of the immune system, and researchers speculate that thymic irregularities are involved in the progression of MG. A definite relationship exists between MG and thymoma: of patients with MG, 15% also have thymoma, and of patients with thymoma, 50% have MG.

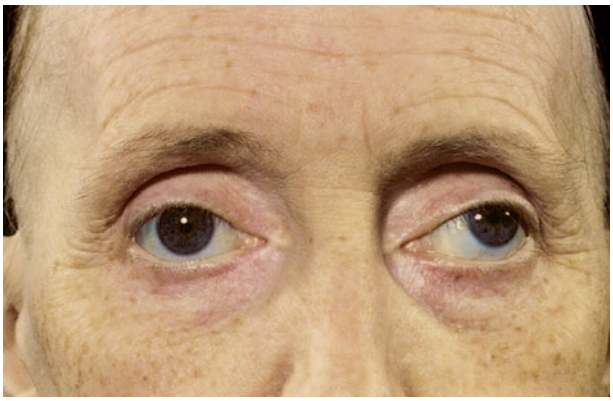
Treatment

While there is no cure for myasthenia gravis, there are a number of treatments that effectively control symptoms in most people. Even though no rigorously tested treatment trials have been reported and no clear consensus exists on treatment strategies, MG is one of the most treatable immune disorders. Several factors require consideration before initiating treatment, such as the severity, distribution, and rapidity of the MG progression.

Edrophonium (Tensilon) is a drug used to block the action of acetylcholinesterase, prolonging the effect of acetylcholine and increasing strength. An injection of edrophonium rapidly leads to a marked improvement in most people with MG. An alternate drug, neostigmine, may also be used.

Pyridostigmine (Mestinon) is usually the first drug tried. Like edrophonium, pyridostigmine blocks acetylcholinesterase. It is longer-acting, taken by mouth, and well-tolerated. Loss of responsiveness and disease progression combine to eventually make pyridostigmine ineffective in tolerable doses in many patients.

Thymectomy, or removal of the thymus gland, has increasingly become a standard form of treatment for MG. Up to 85% of people with MG improve after thymectomy, with complete remission eventually seen in about 30%. The improvement may take months or even several years to fully develop. Thymectomy is not usually recommended for children with MG, since the thymus continues to play an important immune role throughout childhood.



Face of a person afflicted with myasthenia gravis. Half of patients with thymoma (a cancer of the thymus) also have myasthenia gravis. *(Custom Medical Stock Photo. Reproduced by permission.)*

KEY TERMS

Antibody—An immune protein normally used by the body for combating infection and which is made by B cells.

Atropine—An alkaloid extract from belladonna.

Autoantibody—An antibody that reacts against part of the self.

Autoimmune disease—A disease caused by a reaction of the body's immune system.

Bulbar muscles—Muscles that control chewing, swallowing, and speaking.

Immunoglobulin—A protein substance produced by plasma cells which helps to fight infection.

Malignant thymoma—A disease in which cancer cells are found in the tissues of the thymus, a small organ that lies under the breastbone.

Neuromuscular junction—The site at which nerve impulses are transmitted to muscles.

Pyridostigmine bromide (Mestinon)—An anticholinesterase drug used in treating myasthenia gravis.

Tensilon test—A test for diagnosing myasthenia gravis. Tensilon is injected into a vein and, if the person has MG, muscle strength will improve for about five minutes.

Thymectomy —Removal of the thymus by surgery, radiation or chemical means

Thymus gland—A small gland located just above the heart, involved in immune system development.

Immune-suppressing drugs are used to treat MG if patient response to pyridostigmine and thymectomy is not adequate. These drugs include **corticosteroids** such as prednisone, and the non-steroids **azathioprine** (Imuran) and cyclosporine (Sandimmune).

Plasma exchange may also be performed to treat the condition or to strengthen very weak patients before thymectomy. In this procedure, blood plasma is removed and replaced with purified plasma free of autoantibodies. It can produce a temporary improvement in symptoms, but is too expensive for long-term treatment. Another blood treatment, intravenous immunoglobulin therapy, is also used. In this procedure, large quantities of purified immune proteins (immunoglobulins) are injected. For unknown reasons, this leads to symptomatic improvement in up to 85% of patients. It is also too expensive for long-term treatment. There are indications that IVIg is an effective immunoglobulin for some categories of MG patients.

People with weakness of the bulbar muscles may need to eat softer foods that are easier to chew and swallow. In more severe cases, it may be necessary to obtain nutrition through a feeding tube placed into the stomach (gastrostomy tube).

Alternative and complementary therapies

No alternative therapies have been shown to be effective for the treatment of MG. Reports claiming that herbal remedies or alternative treatments alleviate or cure MG have not been corroborated by properly controlled **clinical trials**, which are required to evaluate the benefit of such treatments.

Among complementary MG therapies, prescription of low dose atropine can help relieve the cramping and **diarrhea** often caused by the drug Mestinon. Propantheline bromide (ProBanthine) is a drug similar to atropine, and it may also be prescribed to treat gastrointestinal discomfort. Caution must be taken not to take too much atropine because it cancels the beneficial effects of the anticholinesterase drugs. Ephedrine is sometimes also used with anticholinesterase therapy to strengthen the muscle tissue of MG patients.

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Mycophenolate mofetil

Definition

Mycophenolate mofetil (brand name CellCept) is a drug that has been shown to inhibit tumor growth in rodents, and that may prove useful in treating tumors in humans.

Purpose

The Food and Drug Administration (FDA) approved the use of mycophenolate mofetil in August 2000 for use in patients undergoing liver transplants, and the drug is used primarily to ease the acceptance of a transplanted organ by a recipient. The drug makes acceptance of the transplanted organ more likely because it prevents the recipient from mounting an **immune response** to the organ, or treating it like a foreign invader. The drug also seems to have the ability to inhibit tumor growth, and may prove effective in treating certain kinds of cancer.

In laboratory studies, mycophenolate mofetil has inhibited tumor growth in cancers of the pancreas, colon, lung, and blood. The value of the drug for anticancer therapy is still being evaluated.

In addition to its use in treating cancer, mycophenolate mofetil has been used by dermatologists to treat pyoderma gangrenosum, a rare skin disorder of unknown origin characterized by ulcerated areas on the legs. Pyoderma gangrenosum is associated with systemic diseases in about half the patients diagnosed with it, and mycophenolate mofetil has been found to be effective in treating these patients either alone or in combination with prednisone.

Mycophenolate mofetil is reported to be effective in relieving pain in patients with cluster headache; however, this use of the drug is considered investigational as of 2004.

Description

Mycophenolate mofetil suppresses, or prevents activity of, cells in the lymphatic system, both T cells and B cells. Under normal circumstances, T cells mount an immune response by reacting directly with foreign materials in the body and B cells release compounds that attack foreign materials. But during a transplant, T cells and B cells can cause a reaction that leads to the rejection of a donor organ.

Recommended dosage

The drug is given orally and by intravenous line. Dosages given for cancer therapy are experimental. To prevent immune response during organ transplants, the drug is dispensed in capsules of 250 mg, tablets of 500 mg, and by intravenous line in doses of 500 mg. Time intervals between dosages are determined according to the rate of the drug's breakdown in the patient's body.

Precautions

Mycophenolate mofetil is known to cause or may cause lymphomas and skin cancer. The benefit of taking the drug must be weighed against the increased risk of the cancers it causes.

It is critical for the patient's doctor to monitor blood levels carefully when using this drug, as patients vary widely in their rate of clearance of mycophenolate mofetil, particularly when it is given in combination with other immunosuppressants.

Side effects

In addition to increasing the risk of lymphomas and skin cancer, mycophenolate mofetil may cause a number of other unwanted reactions. They include dizziness, headache, trembling, as well as pain in the chest, swelling (edema), and high blood pressure (hypertension). Many digestive tract upsets from constipation to **diarrhea** to vomiting are also possible side effects. There is also a chance of hemorrhage, or uncontrolled bleeding in the digestive tract.

Interactions

Taking the drug is likely to make oral contraceptives ineffective and another form of birth control should be used. Stomach medications that contain magnesium and aluminum hydroxides, such as antacids, can block the uptake of mycophenolate mofetil across the gut. They should be avoided. As always, the physician in charge of the care plan should be told of every drug a patient is taking so that the potential for interactions can be avoided. The drug is considered superior to some others used as a suppressant of the immune response in transplants because it does not show as many drug interactions as other drugs do. But the short list of interactions might be

KEY TERMS

B cell—A type of cell in the lymphatic system that contributes to immunity by releasing compounds that attack foreign bodies, such as bacteria and viruses.

Clearance—A measure of the rate at which a drug or other substance is removed from the blood.

Intravenous line—A tube that is inserted directly into a vein to carry medicine directly to the blood stream, bypassing the stomach and other digestive organs that might alter the medicine.

Kilogram—Metric measure that equals 2.2 pounds.

Lymphatic system—The system that collects and returns fluid in tissues to the blood vessels and produces defensive agents for fighting infection and invasion by foreign bodies.

Milligram—One-thousandth of a gram, and there are one thousand grams in a kilogram. A gram is the metric measure that equals about 0.035 ounces.

Mutant—Altered, not normal.

T cell—A cell in the lymphatic system that contributes to immunity by attacking foreign bodies, such as bacteria and viruses, directly.

in part related to its limited time on the market, and interactions that are yet unidentified.

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ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657-3000. <www.ashp.org>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

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Mycosis fungoides

Definition

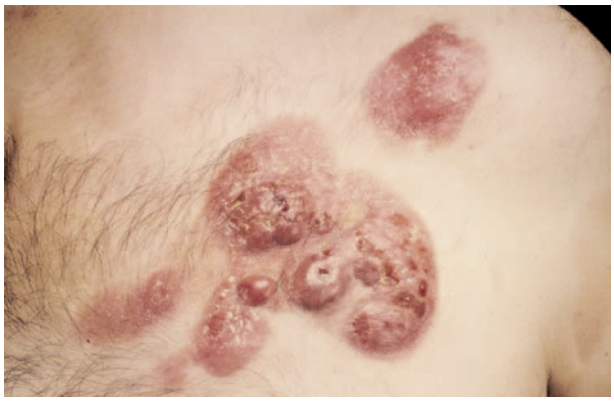
Mycosis fungoides is a skin cancer characterized by patches, plaques, and tumors where cancerous T lymphocytes have invaded the skin.

Description

Mycosis fungoides, the most common type of **cutaneous T-cell lymphoma**, originates from a type of white blood cell called a T lymphocyte or T cell. In mycosis fungoides, cancerous T cells accumulate in the skin. These cells and the skin irritation they create become visible as growths or changes in the skin's color or texture.

Mycosis fungoides usually develops and progresses slowly. It often begins as an unexplained rash that can wax and wane for years. Whether this stage represents early mycosis fungoides or a precancerous stage is controversial. The classic symptoms of mycosis fungoides are red, scaly skin patches that develop into raised plaques, then into large, mushroom-shaped tumors. The patches often originate on parts of the body that are covered by clothing and sometimes improve when they are exposed to sunlight. **Itching** can be intense.

As the cancer progresses, the cancer cells lose their affinity for the skin and spread to nearby lymph nodes and other internal organs. The normal T cells also start to disappear. Because T cells are very important in immunity, this leaves the patient susceptible to infections. Treatment at an earlier stage of the disease can often stop or slow this progression.



Red, scaly plaque on skin of patient with mycosis fungoides. *(Custom Medical Stock Photo. Reproduced by permission.)*

Sézary syndrome is a variant of mycosis fungoides. Sézary syndrome is characterized by red, thickened skin and large numbers of cancer cells in the blood.

Demographics

Mycosis fungoides is usually diagnosed after the age of 50, but has been seen as early as childhood. Mycosis fungoides develops twice as often in men as in women and is more common in people of African than of European origin.

Causes and symptoms

Environmental chemicals, virus infections, allergies, and genes have all been suggested as possible causes of this cancer. As of 2001, there is little concrete evidence to favor any of these possibilities.

The symptoms of mycosis fungoides include:

- Patches: patches are red or brown, sometimes scaly, flat areas. There may be one patch or many. Patches may itch and can resemble psoriasis, eczema, allergies, or other skin diseases. Some patients do not have a patch stage.
- Plaques: plaques are red or brown, sometimes scaly, raised areas. Itching is usually more intense than during the patch stage. The hair sometimes falls out in the affected skin. If the face is involved, the facial features can change.
- Tumors: tumors can originate from plaques, red skin, or normal skin. They are usually reddish brown or purple. The itching can diminish, but the tumors may develop painful open sores or become infected. Some tumors can become very large. Patches, plaques, and tumors can co-exist.
- Erythrodermic form: in the erythrodermic form, the skin becomes red, thickened, and sometimes peels and flakes. The palms and soles thicken and may crack. Itching is usually intense. More than 90% of the time, the erythrodermic form is associated with Sézary syndrome.
- Other, more rare symptoms are also seen, including itching alone.

Diagnosis

A physical examination, history of the symptoms, blood tests, and skin **biopsy** are usually the key to diagnosing this cancer. The blood tests examine the health of the internal organs and look for cancer cells in the blood. The skin biopsy checks for the typical microscopic changes seen in this disease. This biopsy is a brief, simple procedure often done in the doctor's office. After numbing the skin with an injection of local anesthetic, the doctor snips out one or more tiny pieces of abnormal skin. The skin samples are sent to a trained pathologist for examination, and results may take up to a week to come back.

During its early stages, mycosis fungoides can be very difficult to diagnose. The symptoms resemble other skin diseases and numerous biopsies may be needed before the typical features are found. Special stains and DNA tests on the skin sample may find the cancer a little earlier.

To stage this cancer, the lymph nodes are checked for abnormal size or texture and, if necessary, biopsied. The doctor may also recommend x-ray studies of the chest, **computed tomography**, or biopsies of the internal organs to look for cancer cells.

Treatment team

Patients diagnosed with mycosis fungoides are often referred to an oncologist. A dermatologist may also become involved. Depending on the treatment chosen, the team may include other specialists, such as a radiation oncologist, specially trained nurses, a dietitian, or a social worker.

Clinical staging, treatments, and prognosis

Staging

In stage I, the lymph nodes look normal and cancer cells cannot be found in the internal organs. In stage IA, patches or plaques cover less than 10% of the skin. In stage IB, they are present on more than 10%.

In stage IIA, some of the lymph nodes look swollen or abnormal. Patches or plaques may cover any amount of skin. In stage IIB, the lymph nodes may or may not look abnormal, but there is at least one tumor on the

skin. Neither the lymph nodes nor the internal organs contain detectable cancer cells in stage IIA or IIB.

In stage III, the skin looks thickened, red and sometimes scaly. The lymph nodes sometimes look abnormal, but no cancer cells can be detected in them or within internal organs.

In stage IVA and IVB, the skin may have patches, plaques, tumors, or widespread reddening. In stage IVA, cancer cells have been found in the lymph nodes but not in other internal organs. In stage IVB, cancer cells have been found in internal organs and sometimes the lymph nodes.

Treatment

Mycosis fungoides is rarely cured. Instead, most treatments are aimed at controlling the symptoms, improving the quality of life, and preventing the disease from progressing into later stages. This cancer responds well to a variety of therapies and frequently goes into remission, particularly if it is caught early. Even in stage IV, treatment can significantly improve the symptoms in the skin.

In stages III and IV, treatments directed against the cancer cells in the skin may be combined with **chemotherapy** or other therapies against metastatic cells. Experimental treatments are sometimes offered, especially in stage III or stage IV. If the cancer relapses, retreatment may be possible or other therapies can be tried.

One treatment option for early cancers is ultraviolet B (UVB) light. UVB light can treat mycosis fungoides patches, but not plaques or tumors. About 70% of patients go into complete remission and 15% into partial remission. The side effects can include itching, sunburn, aging of the skin, and a risk of developing other skin cancers. The eyes must be protected from UVB light.

Psoralen and ultraviolet A (PUVA) photochemotherapy is an option for all stages, although earlier stages usually have a better response. In PUVA, the drug methoxypsoralen is taken before exposure to ultraviolet A (UVA) light. The drug sensitizes the cancer cells to the light. The complete remission rate with this treatment is 62–90%. The side effects may include itching, dry skin, sunburn, nausea, nail discoloration, and a risk of developing other skin cancers. The eyes must be protected to prevent damage to the retina and possibly cataracts.

Total skin electron-beam irradiation (TSEB) is also effective for all stages. TSEB is a type of radiation treatment that uses beams of electrons to irradiate the skin. The electrons stop at the skin and do not penetrate deeper tissues. Up to 80% of patients in stages II and III will respond. The side effects can include flaking of the skin, alopecia or hair loss (usually temporary), loss of sweat glands, skin irritation, blisters, dryness, temporary loss of the nails, and a risk of developing other skin cancers. These side effects limit the number of times this treatment can be given. TSEB is not available everywhere.

Other types of radiation—for instance, focused electron beam irradiation or x rays—can shrink or destroy some tumors or plaques.

Mechlorethamine (nitrogen mustard) is a drug that can be painted onto the skin to suppress the cancer. A thin layer is applied to the whole skin at bedtime, then washed off in the morning. The side effects can include dryness, skin irritation, darkening of the skin, allergies to the ingredients, and possibly a risk of other skin cancers. Half to 80% of mycosis fungoides patients in stage IA and 25–75% of patients in stage IB or IIA go into complete remission. In stage IIB, the complete remission rate is up to 50%. In stage III, it is 20–40% and, in stage IV, up to 35%. In stages III and IV, this treatment is used to decrease the skin symptoms and is often combined with other treatments.

Carmustine (BCNU) is an alternative drug. Its effectiveness is similar to mechlorethamine. In addition to side effects in the skin, this drug may cause **myelosuppression**.

Bexarotene is a drug used for cases that do not respond to other treatments. About 40% of patients have a complete or partial remission. The side effects may include dryness of the mucous membranes, aching joints or muscles, headaches, **fatigue**, and increased fragility of the skin. One of the most serious side effects is an increase in the fats in the blood, which can lead to pancreatitis.

Aldesleukin fusion toxin contains a poison that damages cells, attached to a molecule that directs that poison to T cells. About 10% of patients have complete remissions and 40% respond to some extent. The side effects can include chills, nausea, fluid retention, and allergic reactions to the drug.

Chemotherapy is sometimes combined with other therapies for stages III and IV. In stage IV, chemotherapy is directed against the metastatic cells in the lymph nodes or internal organs. Approximately 60% of mycosis fungoides patients in stage IV respond to single drugs, but the remission usually lasts less than six months. No cures have been reported, and it is not certain whether chemotherapy lengthens survival.

Corticosteroids are sometimes added to other treatments. These drugs decrease skin irritation and can destroy T cells. Fifty percent of patients have complete

KEY TERMS

Acyclovir—A drug used to kill viruses.

Antibody—A protein made by the immune system. Antibodies attach to target molecules and can be useful as drugs.

Biopsy—A sample of an organ taken to look for abnormalities. Also, the technique used to take such samples.

Computed tomography (CT)—A special x-ray technique that produces a cross-sectional image of the body.

Cutaneous T-cell lymphoma—A type of skin cancer originating from T lymphocytes.

Electron beam—A type of radiation composed of electrons. Electrons are tiny, negatively charged particles found in atoms.

Hypericin—A chemical derived from plants that kills cells after being activated by visible light.

Interferon alpha—A chemical made naturally by the immune system and also manufactured as a drug.

Local anesthetic—A liquid used to numb a small area of the skin.

Lymph node—A small organ full of immune cells that are found in clusters throughout the body. Lymph nodes are where reactions to infections usually begin.

Myelosuppression—A decrease in blood cell production from the bone marrow. This can result in anemia, an increased risk of infections, or bleeding tendencies.

Oncologist—A doctor who specializes in the treatment of cancer.

Pancreatitis—Inflammation of the pancreas. This disease is potentially serious and life-threatening.

Pathologist—A doctor who specializes in examining cells and other parts of the body for abnormalities.

Precancerous—Abnormal and with a high probability of turning into cancer, but not yet a cancer.

Remission—A decrease in the symptoms of the cancer. In a complete remission, there is no longer any evidence of the cancer, although it may still be there.

Retinoids—Drugs related to vitamin A.

T lymphocyte or T cell—A type of white blood cell. Some T cells, known as helper T cells, aid other cells of the immune system. Other T cells, called cytotoxic T cells, fight viruses and cancer.

Ultraviolet light—Light waves that have a shorter wavelength than visble light, but longer wavelength than x rays. UVA light is closer to visible light than UVB.

White blood cells—The cells in the blood that fight infections. There are several types of white blood cells. Also called immune cells.

remissions on corticosteroids and 40% have partial remissions.

Supportive therapies can also help. Antihistamines or other drugs can decrease the itching. Mild moisturizing soaps and moisturizers can also combat the dryness and itching. If infection sets in, **antibiotics** may be necessary.

Prognosis

If mycosis fungoides is caught early, the prognosis is very good. If treatment begins during stage IA, most patients can expect to live as long as someone of the same age and gender who does not have this cancer. Median survival in stage IA is at least 20 years and most people die of diseases unrelated to the cancer. The overall 5-year survival in stage I is 80–90%. In stage II, five-year survival is 60–70%. As tumors develop and the cancer cells spread internally, the prognosis becomes worse. Five-year survival drops to 30% in stage IIB, 40–50% in stage III, and 25–35% in stage IV. Cancer cells can spread into almost any organ in the later stages of mycosis fungoides. Once this happens, many patients die of cancer complications, particularly skin infections that spread into the blood. Overall, half of mycosis fungoides patients live for at least 10 years after their cancer is diagnosed.

Alternative and complementary therapies

Complementary treatments can decrease stress, reduce the side effects of cancer treatment, and help patients feel more in control. For instance, some people find activities such as biofeedback, hypnosis, pet therapy, yoga, massage, pleasant distractions, meditation and prayer, mild physical exercise, or visualization helpful. Patients should check with their doctors before starting any complementary or

QUESTIONS TO ASK THE DOCTOR

- What stage is my cancer?
- If it is treated, is my cancer likely to progress?
- Which treatment(s) do you recommend?
- What are the side effects of these treatments?
- Can you recommend anything to help with those side effects?
- How should I prepare for the treatment?
- Are there any other treatments which might work as well?
- Do you expect me to go into remission and, if so, how long can I expect it to last?
- How often should I return for check-ups?

alternative treatment. This is particularly important for alternative treatments that attempt to cure the cancer, boost the immune system, or reduce the side effects of conventional treatments. Some alternative treatments may interfere with the standard medical treatments or be dangerous when they are combined.

Coping with cancer treatment

Many of the treatments used for mycosis fungoides can dry and irritate the skin. Some ways to help are:

- Wear soft, loose clothing over the affected areas.
- Protect the skin from the sun.
- Don't scratch or rub the affected areas.
- Check with a doctor or nurse before using lotions, moisturizers, sunscreens, or cosmetics on the area.
- If allowed, use moisturizer and a moisturizing soap.

Clinical trials

Because mycosis fungoides is unlikely to be cured with the standard treatments, all patients with this disease are candidates for **clinical trials**. Patients should check with their medical insurers before enrolling in a clinical trial. Insurers may not pay for some treatments; however, this varies with the insurer and each individual case.

Some clinical trials are testing new drugs, including some retinoids, acyclovir, and hypericin.

In extracorporeal photochemotherapy, the white blood cells are exposed to a chemical called a psoralen, temporarily separated from the rest of the blood and treated with UVA light, then returned to the body. This treatment may stimulate the immune system to destroy the cancer cells.

Interferon alpha is a drug that is injected into plaques and tumors. About 55% of patients have some response and 17% go into complete remission. The side effects may include fevers, fatigue, loss of appetite (anorexia), decreases in the number of white blood cells, or irregular heartbeats.

Antibodies can block important molecules on the cancer cells or carry poisons or radioactive molecules to the cancer.

Some clinical trials are testing whether **bone marrow transplantation** can produce lasting remissions.

Prevention

The risk factors for mycosis fungoides are unknown and there is no known means of prevention.

Special concerns

Because mycosis fungoides is rarely cured, patients must usually return periodically for check-ups or treatments to maintain the remission. Between visits, patients should also be alert for skin infections. These infections can spread into the blood and become serious if they are not controlled. Because mycosis fungoides can affect the appearance, patients may wish to discuss cosmetic concerns with a doctor, other professional, or support group. Mycosis fungoides increases the risk of developing other types of lymphocyte cancers.

See also Body image; Lymph node biopsy.

Resources

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The Cutaneous Lymphoma Network. Judi Van Horn, R.N., Editor. c/o Department of Dermatology, University of Cincinnati, P.O. Box 670523, Cincinnati, OH 45267-0523. (513) 558-6805. This organization produces a newsletter with articles on this cancer, information on support groups, and opportunities for contact with other mycosis fungoides patients.

The Mycosis Fungoides Foundation. P.O. Box 374, Birmingham, MI, 48102-0374. (248) 644-9014. <http://MFFoundation.org>.

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Myelodysplastic syndrome

Definition

Myelodysplastic syndrome (MDS) is a disease that is associated with decreased production of blood cells. Blood cells are produced in the bone marrow, and the blood cells of people with MDS do not mature normally. There are three major types of blood cells—red blood cells, white blood cells and platelets. Patients with MDS can have decreased production of one, two, or all three types of blood cells.

Description

Overview

Blood cells are used in the body for many different and important functions, such as carrying oxygen (red blood cells), fighting infection (white blood cells), and controlling bleeding (platelets). Blood cells are formed and stored in the bone marrow, which is the spongy tissue inside large bones. Stem cells, or immature blood cells, are stored in the bone marrow and have the ability to develop into all three types of mature blood cells. When the body needs a specific type of blood cell, the bone marrow uses its stockpile of stem cells to produce the kind of mature cells needed for that particular situation.

In patients who have MDS, blood cells fail to mature normally. In other words, the bone marrow is unable to develop a normal amount of mature blood cells, and is also not able to increase blood cell production when mature cells are needed. Sometimes, even the cells that are produced do not function normally. The marrow eventually becomes filled with the immature cells (blasts) and there is not room for the normal cells to grow and develop. MDS therefore causes a shortage of functional blood cells.

Subtypes of MDS

MDS is divided into five different subtypes that are classified according to the number and appearance of blast cells in the bone marrow. It is important for doctors to know the type of MDS a patient has, because each subtype affects patients differently and requires specific treatment. The International Prognostic Scoring System (IPSS) can help the doctor to determine the best treatment for an individual patient. The subtypes are as follows:

- Refractory **anemia** (RA). Bone marrow with less than 5% blast cells and abnormal red blood cell blasts.
- Refractory anemia with ring sideroblasts (RARS). Bone marrow with less than 5% blasts and characteristic abnormalities in red blood cells.
- Refractory anemia with excess blasts (RAEB). Bone marrow with 5-20% blast cells, and higher risk of changing into **acute leukemia** over time.
- Refractory anemia with excess blasts in transformation (RAEBT). Bone marrow with 21-30% blast cells. This form is most likely to change into acute leukemia.
- Chronic myelomonocytic leukemia (CMMoL). Marrow with 5-20% blasts and excess monocytes (a specific type of white blood cell).

Demographics

Approximately 15,000 new cases are diagnosed annually in the United States. The average age at diagnosis is 70. The most common types are RA and RARS. It is rare to have MDS before age 50. MDS is slightly more common in males than in females.

Causes and symptoms

Causes

There is no clear cause for the majority of MDS cases, which is referred to as primary or *de novo* myelodysplastic syndrome. In some cases, however, MDS results from earlier cancer treatments such as radiation and/or **chemotherapy**. This type of MDS is called secondary or treatment related MDS, is often seen three to seven years after the exposure, and usually occurs in younger people.

Other possible causative agents for MDS include exposure to radiation, cigarette smoke or toxic chemicals such as benzene. Children with pre-existing chromosomal abnormalities such as Down syndrome have a higher risk of developing MDS. MDS does not appear to run in families, nor can it be spread to other individuals.

Symptoms

MDS symptoms are related to the type of blood cells that the body is lacking. The earliest symptoms are usually due to anemia, which results from a shortage of mature red blood cells. Anemia causes patients to feel tired and out of breath because there is a lack of cells transporting oxygen throughout the body. MDS may also lead to a shortage of white blood cells resulting in an increased likelihood of infections. Another symptom of MDS is increased bleeding (e.g. blood in stool, nose bleeds, increased bruises or bleeding gums) which is due to low level of platelets. These symptoms can occur in any combination, depending on a given patient's specific subtype of MDS.

Diagnosis

Blood tests

People who have MDS usually visit their primary care doctor first, with symptoms of **fatigue**, and are then referred to a hematologist (a physician who specializes in diseases of the blood). The diagnosis of MDS requires a complete analysis of the patient's blood and bone marrow, which is done by the hematologist. A complete blood count (CBC) is done to determine the number of each blood cell type within the sample. Low numbers of red blood cells, white blood cells, and or platelets are signs that a patient has MDS. Numerous other medical problems such as bleeding, nutritional deficiencies, or adverse reaction to a medication can also cause low blood counts. The hematologist will investigate other causes for low blood counts before assigning a diagnosis of MDS. Blood cells in patients with MDS can also be abnormal when viewed under the microscope.

Bone marrow aspiration and biopsy

A bone marrow **biopsy** is required to confirm the diagnosis of MDS and determine the correct MDS subtype. This procedure involves a needle used to take a sample of marrow from inside the bone. The area of the skin where the needle is inserted is numbed and sometimes the patient is also sedated. Patients may experience some discomfort but the procedure is safe and is over fairly quickly. Marrow samples are usually taken from the back of the hip bone (iliac crest). A sample of the marrow, known as an aspirate, and a small piece of bone are both removed with the needle.

A hematologist or a pathologist (a specialist in diagnosing diseases through cell examination) will carefully examine the bone marrow sample through a microscope. Microscopic examination allows the doctor to determine the number and type of blast cells within the marrow in order to identify the MDS subtype. Cells from the bone marrow are also sent for cytogenetic testing, which analyzes the cells' chromosomes. Forty to seventy percent of MDS patients have abnormal bone marrow chromosomes as a result of the disease. The pattern of these abnormalities can be used to predict how a patient will respond to a particular treatment. Thus, the full set of information provided by a bone marrow biopsy and CBC will ultimately allow the doctor to recommend the most effective treatment plan.

Clinical staging, treatments, and prognosis

International Prognostic Scoring System (IPSS) for MDS

Once a diagnosis of MDS is established, the doctor will calculate the IPSS score for each individual patient. The bone marrow blast percentage, chromosomal abnormalities and number of different blood types that are reduced determine the score. A score of 0 to 3.5 is assigned to each patient. Patients with lower score have a better prognosis and usually should not undertake treatment upon initial diagnosis. Patients with a higher score have more aggressive disease and should consider more aggressive treatment.

Treatments

SUPPORTIVE CARE Treatment for MDS is tailored to the patient's age, general health, specific MDS subtype, and IPSS score. Treatment varies for each patient, but most treatment strategies are designed to control the symptoms of MDS. This approach is called supportive care and aims to improve the patient's quality of life.

Supportive care for the MDS patients commonly includes red blood cell transfusions to relieve symptoms related to anemia. Red cell transfusions are relatively

safe and the physician will review risks and benefits with this approach. Transfusions of any type only last a certain amount of time and therefore need to be repeated at certain intervals. Platelet transfusions can also be a way to control excessive bleeding. The doctor will decide with each individual patient when it is appropriate to give a transfusion. **Antibiotics** are used when needed to combat infections that can occur more frequently in patients with low white blood cell counts.

BONE MARROW TRANSPLANTATION **Bone marrow transplantation** (BMT) is a type of treatment that attempts to provide MDS patients with a cure. This strategy requires the patients to be in fairly good health and are therefore more likely to be used in younger patients. Bone marrow transplantation (BMT) has been found to be a successful treatment for MDS patients under the age of 50 (and some over 50 in good health). Following BMT, many patients are able to achieve long-term, disease-free survival. Unfortunately, most MDS patients cannot receive a traditional bone marrow transplant because of older age or because they do not have a suitable donor. Bone marrow donors are usually siblings or are obtained from the national bone marrow registry. "Mini"-bone marrow transplants use less intense chemotherapy, and are currently being tested in older patients who would otherwise not be candidates for traditional bone marrow transplants.

CHEMOTHERAPY Chemotherapy has been used to treat some MDS patients; however, the disease often recurs after a period of time. This type of therapy uses cell-killing drugs that may also damage healthy cells in the body. Most chemotherapy drugs are associated with some side effects. For these reasons, chemotherapy is generally not used until the MDS becomes more aggressive or the patient has a high IPSS score.

GROWTH FACTORS Growth factors are natural proteins that the body normally uses to control blood production. These substances stimulate the patient's bone marrow to produce healthy blood cells. Growth factors that stimulate white cell production are G-CSF (also called neupogen or **filgrastim**) and GMCSF (Leukine, **sargramostim**). In order to increase red cell production another growth factor, **erythropoietin** (Procrit) is used. These growth factors are safe with few side effects and are available only in the injectable form. The physician will decide if this treatment is appropriate for an individual patient.

Prognosis

The prognosis for MDS patients depends on the subtype of their disease and the IPSS score. Patients with RA, RARS or low IPSS score rarely develop leukemia and may live with disease for some years. The higher-risk patients including those with RAEB, RAEBt, CMMoL or high IPSS scores progress more rapidly, and require intensive therapy to control the disease.

Managing MDS requires frequent doctor appointments to monitor disease progression and to evaluate the response to treatment. Fortunately for many patients, recent advances in therapy have significantly enhanced their ability to cope with MDS. Experimental drugs and a better understanding of the disease are likely to improve the overall prognosis in the future.

Alternative and complementary therapies

There are no alternative therapies that have been proven to successfully treat MDS. Some of the available alternative drugs can have adverse side effects and therefore a physician should be informed if they are being used.

Clinical trials

Many **clinical trials** are available for MDS patients. These trials are testing new drugs or procedures in this condition. These treatments have not yet been proven to have success in this condition, but the principal investigators are hopeful that patients will benefit. The physician can discuss appropriate clinical trials with interested patients. Trials can involve new chemotherapy drugs, low-dose bone marrow transplantation and novel non-chemotherapy drugs. It is important for a patient to thoroughly understand the risks (listed in the consent form) before signing up for such treatments.

Prevention

MDS is usually impossible to prevent. Being careful about daily activities and avoiding the use of aspirin-like products that thin the blood may prevent secondary complications of MDS such as bruising and bleeding. Practicing good hygiene and avoiding crowds or people with infections can sometimes prevent infections. A well-balanced diet is recommended to increase overall energy.

Special concerns

MDS is the subject of extensive research, and new treatments are under development. In addition to treatment by their local hematologist or oncologist, motivated patients can pursue experimental treatments at major medical centers.

Resources

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ORGANIZATIONS

Aplastic Anemia Foundation of America. P.O. Box 613, Annapolis, MD 21404. (800)747-2820. <www.aplastic.org>.

Leukemia Society of America. 600 Third Avenue, New York, NY 10016. (800)955-4LSA. < www.leukemia.org>.

Myelodysplastic Syndromes Foundation. 464 Main Street, P.O. Box 477, Crosswicks, NJ 08515. (800) MDS-0839. <www.mds-foundation.org>.

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Myelofibrosis

Definition

Myelofibrosis is a rare disease of the bone marrow in which collagen builds up fibrous scar tissue inside the marrow cavity. This is caused by the uncontrolled growth of a blood cell precursor, which results in the accumulation of scar tissue in bone marrow. Myelofibrosis goes by many names including idiopathic myelofibrosis, agnogenic myeloid metaplasia, chronic myelosclerosis, aleukemic megakaryocytic myelosis, and leukoerythroblastosis.

Description

Myelofibrosis can be associated with many other conditions including **breast cancer**, **prostate cancer**, **Hodgkin's disease**, **non-Hodgkin's lymphomas**, acute myelocytic leukemia, **acute lymphocytic leukemia**, **hairy cell leukemia**, **multiple myeloma**, **myeloproliferative diseases**, tuberculosis, Gaucher's disease, and Paget's disease of bone. Myelofibrosis typically becomes progressively worse and can cause death.

In myelofibrosis, abnormal cells (hematopoietic stem cells) grow out of control and begin to produce both immature blood cells and excess scar (fibrous) tissue. The fibrous tissue builds up (fibrosis) primarily in the bone marrow, the place where blood cells are produced. The fibrous tissue interferes with the production of normal blood cells. The outcome of this is that the blood made by the bone marrow is of poor quality. To compensate for this, blood cell production occurs in other parts of the body (extramedullary hematopoiesis), but most notably in the spleen and liver. This causes enlargement of the spleen (splenomegaly) and the liver (hepatomegaly). Extramedullary hematopoiesis is not effective and, combined with the reduced production of blood cells by the bone marrow, a condition called **anemia** results.

The abnormal stem cells can spread throughout the body, settle in other organs, and form tumors that produce more abnormal blood cells and fibrous tissue. These tumors are most commonly found in the adrenals, kidneys, lymph nodes, breast, lungs, skin, bowel, thymus, thyroid, prostate, and urinary tract.

Demographics

Most patients with myelofibrosis are over 50 years old; the average age at diagnosis is 65 years. However, myelofibrosis can occur at any age. Myelofibrosis occurs with equal frequency in women and men, but in children it affects girls twice as often as it does boys.

Causes and symptoms

Myelofibrosis is caused by an abnormality in a single stem cell, which causes it to grow out of control. Myelofibrosis tumors that have originated from a single cell are called monoclonal. The cause of the stem cell abnormality is unknown. Persons who were exposed to benzene or high doses of radiation have developed myelofibrosis. There may be an association between myelofibrosis and autoimmune diseases, such as systemic lupus erythematosus and scleroderma, in which the immune system treats certain molecules of the body as foreign invaders.

Symptoms usually appear slowly over a long period of time. About one quarter of all patients with myelofibrosis have no symptoms (asymptomatic). An enlarged spleen discovered at an annual medical examination may be the first clue. Symptoms of myelofibrosis include:

- fatigue
- weight loss
- paleness
- fever
- sweating
- weakness
- heart palpitations
- shortness of breath
- itching
- feeling full after eating a small amount of food
- stomach pain or discomfort
- pain in the left shoulder or upper left portion of the body

- unexpected bleeding
- **bone pain**, especially in the legs

Diagnosis

Because symptoms are similar to other diseases (mostly leukemias), myelofibrosis is not easy to diagnose. The doctor would use his or her hands to feel (palpate) for enlargement of the spleen and liver. Blood tests and urine tests would be performed. **Bone marrow aspiration and biopsy** can help make a diagnosis, but they often fail because of the fibrosis. X-ray imaging and **magnetic resonance imaging** (MRI) may be performed.

Treatment

Many asymptomatic patients, if stable, do not require treatment. There is no cure for myelofibrosis, although **bone marrow transplantation** is curative in some cases. Treatment is aimed at reducing symptoms and improving quality of life.

Medications

Male hormones (androgens) can be used to treat anemia but, in women, these drugs can cause the development of male characteristics (e.g., hair growth on the face and body). Glucocorticoid therapy is also an effective treatment of anemia and can improve myelofibrosis in children. Nutrients that stimulate blood formation (hematinics), such as iron, **folic acid**, and vitamin B_{12}, may reduce anemia. Cancer **chemotherapy** (usually **hydroxyurea**) can decrease splenomegaly and hepatomegaly, reduce symptoms of myelofibrosis, lessen anemia, and sometimes reduce bone marrow fibrosis. The bone marrow of myelofibrosis patients is often not strong enough to withstand the harsh chemotherapy drugs, so this treatment is not always an option. Interferon-alpha has been shown to reduce spleen size, reduce bone pain, and, in some cases, increase the number of blood platelets (structures involved in blood clotting).

Other treatments

In certain cases, the enlarged spleen may be removed (**splenectomy**). Conditions that warrant splenectomy include spleen pain, the need for frequent blood transfusion, very low levels of platelets (**thrombocytopenia**), and extreme pressure in the blood vessels of the liver (portal hypertension).

Radiation therapy is used to treat splenomegaly, spleen pain, bone pain, tumors in certain places such as next to the spinal cord, and fluid accumulation inside the abdomen (**ascites**). Patients who are not strong enough to undergo splenectomy are often treated with radiation therapy.

Bone marrow transplantation may be used to treat some patients with myelofibrosis. This procedure may

KEY TERMS

Anemia—Low numbers of red blood cells in the blood.

Benzene—A colorless volatile flammable toxic liquid hydrocarbon used as a solvent and as a motor fuel.

Biopsy—Surgical removal of tissue for microscopic examination.

Fibrosis—Buildup of scar tissue.

Glucocorticoid therapy—Treatment using corticoids that are anti-inflammatory and immunosuppressive.

Leukemia—Cancer of white blood cells.

Portal hypertension—Extreme pressure on the blood vessels of the liver.

Stem cell—A cell that has the ability to become many different specialized cells.

be performed on patients who are less than 50 years old, have a poor life expectancy, and have a brother or sister with blood-type similarities.

Patients with severe anemia may require blood transfusions.

Prognosis

Similar to leukemias, myelofibrosis is progressive and often requires therapy to control the disease. Myelofibrosis can progress to acute lymphocytic leukemia or lymphoma. Although a number of factors to predict the survival time have been proposed, advanced age or severe anemia are consistently associated with a poor prognosis. The average survival rate of patients diagnosed with myelofibrosis is five years. Death is usually caused by infection, bleeding, complications of splenectomy, heart failure, or progression to leukemia. Spontaneous remission is rare.

Prevention

Persons who have been exposed to radiation, benzene, or radioactive thorium dioxide (a chemical used during certain diagnostic radiological procedures) are at risk for myelofibrosis.

Resources

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Myeloma

Definition

Cancer that arises in the bone marrow and involves plasma cells, a type of white blood cell that produces proteins called immunoglobulins.

Myeloproliferative diseases

Definition

The myeloproliferative diseases are four conditions—essential thrombocythemia, polycythemia vera, **chronic myelocytic leukemia**, and agnogenic myeloid metaplasia—characterized by overproduction of normal-looking blood cells.

Because chronic myelocytic leukemia has its own individual entry, it is not covered in depth in this entry.

Description

The prefix "myelo—" refers to marrow. Bone marrow, a reddish substance in the middle of some bones, produces blood cells. In the myeloproliferative diseases, the body makes too many blood cells. Blood contains red blood cells to carry oxygen, white blood cells to fight infections, and platelets to begin blood clotting. Myeloproliferative diseases develop when a myeloid progenitor cell—a cell that makes red blood cells, platelets, and certain types of white blood cells—becomes overactive. The abnormal progenitor cell continues to make normal blood cells, but it makes too many of them. This excess of blood cells results in varying symptoms, depending on the progenitor cell involved.

Other problems develop when some of the abnormal myeloid progenitor cells travel to the spleen, liver, or

lymph nodes and begin making blood cells there. Most often, they migrate to the spleen. An enlarged spleen can crowd other organs in the abdomen and cause discomfort or digestive troubles. It is also susceptible to painful damage from blocked arteries. Massively swollen spleens can use large amounts of energy and cause muscle wasting and **weight loss**.

In the later stages of myeloproliferative diseases, the bone marrow can become scarred. This may leave no space for progenitor cells. As a result, blood cell production can drop to dangerously low levels. The abnormal progenitor cells may also mutate and develop into leukemia. These two serious complications are rare in some myeloproliferative diseases but very common in others.

Types of myeloproliferative disease

The four myeloproliferative diseases include essential thrombocythemia, polycythemia vera, chronic myelocytic leukemia, and agnogenic myeloid metaplasia.

In essential thrombocythemia (primary thrombocythemia), the myeloid progenitor cell makes too many platelets. Blood containing too many platelets may either clot too easily or too slowly. Blood that clots too easily can lead to a variety of health problems, including strokes or heart attacks. Blood that clots too slowly can cause symptoms such as easy bruising, frequent nosebleeds, bleeding from the gums, or life-threatening hemorrhages. Excessive numbers of platelets can also cause headaches or erythromelalgia, an unusual condition characterized by warmth, redness and pain in the hands or feet. Typically, patients with this disease have long periods without symptoms, interspersed with clotting or bleeding episodes. Some patients may have no symptoms at all. Rarely, this disease ends in scarring of the bone marrow or leukemia. Patients with bone marrow scarring have symptoms identical to agnogenic myeloid metaplasia.

In polycythemia vera (primary polycythemia, Vaquez disease), the bone marrow makes too many red blood cells. Large numbers of red blood cells can make the blood too thick. Viscous blood flows sluggishly, pools in the veins, and delivers oxygen poorly. Patients may experience headaches, dizziness, **fatigue**, chest pains, or weakness and cramping in the calves while walking. The abnormal blood flow can also result in bleeding tendencies or blood clotting inside the veins. Many patients also have increased numbers of white blood cells or platelets, but most symptoms are caused by the sluggish blood flow. The spleen often enlarges. Polycythemia rarely leads to leukemia, but occasionally ends in bone marrow scarring.

In chronic myelocytic leukemia (chronic myelogenous leukemia), the myeloid progenitor cell makes a type of white blood cell called a granulocyte. With this condition, platelets can also increase. In the early stages of this disease, the white blood cells look outwardly normal. However, in 90–95% of patients, two chromosomes—number 9 and number 22— inside the progenitor cell have broken and exchanged parts. This chromosome rearrangement is known as the Philadelphia chromosome, and this genetic abnormality destabilizes these cells and inevitably they become cancerous.

Agnogenic myeloid metaplasia (idiopathic **myelofibrosis**, myelofibrosis with myeloid metaplasia) begins like other myeloproliferative diseases, with overproduction of blood cells. However, bone marrow scarring develops very quickly and causes most of the symptoms. Blood cell numbers drop, causing fatigue and weakness from **anemia**. Many of the cells found in the blood are also immature or oddly shaped. Although myeloid progenitor cells in the spleen and liver can partly compensate, the enlargement of these organs creates additional problems. Occasionally, this disease also ends in leukemia.

Demographics

Essential **thrombocytopenia**, polycythemia vera, and agnogenic myeloid metaplasia are usually diagnosed late in life, at an average (median) age of 60.

Essential thrombocythemia may be slightly more common in women and agnogenic myeloid metaplasia and polycythemia vera slightly more common in men; however, estimates vary. At one time, polycythemia vera was thought to develop more often in Jews. More recent statistics do not confirm this.

Causes and symptoms

No consistent chromosomal abnormalities have been discovered in essential thrombocythemia, polycythemia vera, or agnogenic myeloid metaplasia. The causes of these diseases are unknown.

Myeloproliferative diseases share many features, such as enlargement of the spleen and abnormalities in blood clotting. Symptoms that can be seen in any of these diseases include:

- fatigue
- poor appetite (anorexia)
- weight loss
- **night sweats**
- fullness in the stomach after eating only a small amount
- abdominal pain or discomfort, especially in the upper left side

- nosebleeds, bleeding from the gums, easy bruising, or intestinal bleeding
- symptoms of blood clots including strokes, heart attacks, pain and swelling in the legs, or difficulty breathing
- disturbances in vision

Other symptoms of essential thrombocythemia can include:

- weakness
- dizziness
- headaches
- prickling or tingling in the skin
- erythromelalgia (warmth, redness, and pain in the extremities)

Other symptoms of polycythemia vera can include:

- headaches
- dizziness
- ringing in the ears
- pain in the chest (angina)
- weakness or cramping pains in the legs that disappear during rest
- redness of the face
- a blue tinge to the skin and other body surfaces (cyanosis)
- high blood pressure
- **itching**, especially after a warm bath or shower
- tingling or prickling of the skin
- erythromelalgia
- ulcers
- kidney stones
- gout

Other symptoms of agnogenic myeloid metaplasia can include:

- **fever**
- gout
- bone pain

Diagnosis

The diagnosis of a myeloproliferative disease relies mainly on a physical examination, examination of a blood sample, and sometimes a bone marrow **biopsy**. In the blood samples, the doctor will find excessive numbers of the cells characteristic of each disease. Chromosome studies on the blood can often distinguish chronic myelocytic leukemia from the other three diseases. Bone marrow samples reveal increased cell production and sometimes scarring. An enlarged spleen can often be detected during a physical examination, but occasionally ultrasound or **computed tomography** scans may be necessary.

Myeloproliferative diseases can resemble normal reactions to infections and other diseases. Various tests may be done to rule out such diseases.

Clinical staging, treatments, and prognosis

Staging

There is no staging system for essential thrombocythemia, polycythemia vera, or agnogenic myeloid metaplasia.

Treatments

ESSENTIAL THROMBOCYTHEMIA Treatments for essential thrombocythemia lower the risk of bleeding or blood clots. One option is **hydroxyurea** (Hydrea), a drug that suppresses platelet production. Hydroxyurea has few side effects but can occasionally cause a rash, intestinal upsets, sores on the skin, or a fever. This drug may also slightly increase the risk of leukemia. **Anagrelide** (Agrylin), an alternative, is effective in more than 90% of patients. It does not promote leukemia but can cause dizziness, headaches, fluid retention, rapid heartbeats, **diarrhea**, and rare cases of heart failure. Hydroxyurea and anagrelide both increase the risk of miscarriages during the first trimester in pregnant women.

A patient under 60 who has never had a blood clot has a 3% chance of developing one in the future. Some doctors recommend treatment for these patients only during high-risk situations such as surgery. Low doses of aspirin are sometimes used to control symptoms such as erythromelalgia.

POLYCYTHEMIA VERA Periodically removing small amounts of blood, called phlebotomy, is a safe and very effective way to treat polycythemia vera. In some studies, phlebotomy has increased the risk of blood clotting. However, this may not occur when the hematocrit (the percentage of red blood cells in the blood) is kept below 45% in men and 43% in women. Phlebotomy can result in symptoms of iron deficiency such as abnormal food cravings (particularly a craving for ice).

Patients who are unlikely to develop blood clots may not need any other treatments. Patients with a higher risk of clotting are sometimes given hydroxyurea. This drug has relatively few side effects, but it may increase the chance of developing leukemia. In some studies, 3–5% of patients taking hydroxyurea eventually developed leu-

kemia, compared to 1.5–2% treated with phlebotomy alone. Alternatives to hydroxyurea include interferon alpha and anagrelide. These drugs do not increase the risk of leukemia, but they tend to have more side effects. Interferon alpha may be particularly difficult to tolerate. Its side effects include flu-like symptoms (fever, chills, postnasal drip and poor appetite), fatigue, weight loss, **depression**, insomnia, memory loss, and nausea.

Radioactive phosphorus is used mainly in elderly patients who do not expect to need many years of treatment. In 80–90% of patients, this treatment can suppress the disease symptoms for six months to several years. However, up to 17% of patients develop leukemia within 15 years.

Other symptoms of polycythemia vera are treated with a variety of drugs. Itching is sometimes suppressed by phlebotomy, but antihistamines are often needed as well. Other options include extracorporeal photochemotherapy, hydroxyurea, or interferon alpha. **Allopurinol** (Zyloprim) prevents kidney stones and gout. Aspirin can suppress the symptoms of erythromelalgia.

One of the most difficult complications to treat is enlargement of the spleen. In the early stages of the disease, this enlargement can often be controlled by phlebotomy. Later, interferon alpha, hydroxyurea, or surgical removal may be necessary. Surgery to remove a very large spleen is difficult and can be fatal in up to 10% of patients. Complications can include infections, bleeding, serious blood clotting, or increased numbers of white blood cells and platelets. Radiation treatments directed at the spleen may be another option, but they can suppress the bone marrow.

AGNOGENIC MYELOID METAPLASIA Agnogenic myeloid metaplasia can be cured by a bone marrow transplant from a healthy donor. In patients eligible for this treatment, it is successful in about a third. **Bone marrow transplantation** may not be feasible for many patients, particularly those who are older or in poor health. This procedure can have serious or fatal complications including infections, organ damage, and bleeding. In addition, compatible donors are not available for all patients.

Other treatments for this disease are not curative and are mainly intended to improve the quality of life. Anemia is often treated with regular transfusions of red blood cells. Adverse effects can include heart failure or damage to the liver from excess iron. Drugs can sometimes make red blood cells last longer. **Corticosteroids** combined with an androgen (**fluoxymesterone**) are effective in about a third of all patients. **Danazol**, another androgen, works in about 20%. These drugs may damage the liver and can produce masculine traits in women. Injections of **erythropoietin**, a hormone that stimulates red blood cell production, also work in a few patients.

About half of all patients with anemia improve after surgical removal of the spleen (splenectomy). This surgery can also help patients who have abdominal discomfort, weight loss, muscle wasting, or high blood pressure in the liver. However, it can be dangerous and sometimes fatal. Removal of the spleen may make the disease progress more quickly, but this is not certain.

A painfully enlarged spleen can also be treated with hydroxyurea, interferon alpha, or radiation treatments. Hydroxyurea has few side effects, but it may increase the risk of leukemia. Interferon alpha shrinks the spleen in 30–50% of patients, but has many side effects. Radiation treatments can decrease the symptoms for three to six months, but sometimes fatally suppress the blood-producing cells.

Prognosis

Patients with essential thrombocythemia can expect a near normal life-span. Average (median) survival is 12 to 15 years. The chance of developing either leukemia or serious scarring of the bone marrow is less than 5%.

Without treatment, patients with polycythemia vera usually die from bleeding or blood clotting within months. With treatment, average (median) survival is about 10 years in older patients and more than 15 years in younger patients. Many patients can reach their normal life expectancy if they do not develop bone marrow scarring or leukemia. The risk of bone marrow scarring after 10 years is approximately 15–20%. If polycythemia vera is treated with phlebotomy alone, the risk of developing leukemia is 2%.

Unless they receive a successful bone marrow transplant, most patients with agnogenic myeloid metaplasia become progressively worse. The anemia becomes more severe and the liver and spleen continue to swell. Average (median) survival in this disease is 3.5 to 5.5 years, but survival is often unpredictable and may be much longer or much shorter. Leukemia develops in about 5–20% of patients. In other patients, death occurs from heart failure, infections, bleeding or blood clots.

Alternative and complementary therapies

In traditional Chinese and Japanese medicine, herbal preparations are used to treat symptoms of chronic illnesses such as fatigue, loss of appetite, and night sweats, or to decrease red blood cell formation in polycythemia vera. Patients who are interested in non-traditional complementary remedies should discuss them with their doctors. Some may have dangerous side effects or be harmful when combined with traditional therapies.

KEY TERMS

Androgen—A drug related to the male sex hormones.

Autoimmune disease—A disease that develops when white blood cells attack normal cells or organs.

Biopsy—A sample of an organ taken to look for abnormalities. Also, the technique used to take such samples.

Bone marrow—A group of cells and molecules found in the centers of some bones. It makes all of the cells found in the blood.

Computed tomography (CT)—A special x-ray technique that produces a cross-sectional image of the organs inside the body.

Corticosteroids—A class of drugs, related to hormones naturally found in the body, that suppresses the immune system. One example is prednisone, sold under many brand names including Deltasone.

Erythromelalgia—A condition characterized by warmth, redness and pain in the hands and especially the feet.

Erythropoietin—A drug that stimulates the bone marrow to make more red blood cells. It is also known as epoetin alfa.

Extracorporeal photochemotherapy—A technique in which the white blood cells are exposed to a chemical called a psoralen, temporarily separated from the rest of the blood and treated with UVA light, then returned to the body.

Gout—A painful swelling of the joints that results from an accumulation of uric acid. This disease often affects the big toe.

Granulocyte—One of three types of white blood cells (neutrophils, eosinophils, and basophils) that contain visible granules.

Lymph node—A small organ full of white blood cells, found in clusters throughout the body. Lymph nodes are where reactions to infections usually begin.

Median—A type of average. The median is the number in the middle of a sequence of numbers.

Myeloid progenitor cell—A cell normally found in the bone marrow that makes red blood cells, platelets, and some white blood cells (granulocytes and monocytes).

Phlebotomy—The removal of blood.

Platelets—Tiny fragments of cells that begin the blood clotting process. They are found in the blood.

Red blood cells—The cells in the blood that carry oxygen.

Spleen—An organ in the abdomen near the stomach. The spleen makes white blood cells, stores red blood cells, and removes old blood cells from the circulation.

Transfusion—A transfer of blood or blood products from one person to another.

Ultrasound—A technique that uses sound waves to form an image of organs inside the body.

White blood cells—The cells in the blood that fight infections. There are several types of white blood cells. Also known as immune cells.

Coping with cancer treatment

Acetaminophen and antidepressant drugs can help reduce some of the side effects of interferon alpha. Taking this drug at night may also make it easier to tolerate.

Clinical trials

The following therapies are being tested in **clinical trials**. Patients should check with their medical insurers before enrolling in a clinical trial. Insurers may not pay for some treatments but this varies with the insurer and each individual case.

Interferon alpha injections are being tested in essential thrombocythemia. This drug can lower platelet numbers and decrease the size of the spleen in about 80% of patients.

Several new drugs are in clinical trials. **Thalidomide** and SU5416 are being tested in patients with agnogenic myeloid metaplasia. R115777 and 12-O-tetradecanoylphorbol-13-acetate (TPA) are in clinical trials open to patients with various myeloproliferative diseases.

Another possible treatment for agnogenic myeloid metaplasia is to purify the normal progenitor cells and return them to the body after destroying the abnormal progenitor cells with **chemotherapy**.

Prevention

The following environmental factors have been linked to myeloproliferative diseases:

- working as an electrician or in a petroleum manufacturing plant

QUESTIONS TO ASK THE DOCTOR

- Does my condition require treatment?
- What treatment would you recommend I try?
- What risks and side effects should I expect?
- How will it affect my quality of life?
- Are there any alternative treatments that might work equally well?
- Are there any activities I should avoid? For how long?

- prolonged use of dark hair dyes
- exposure to nuclear bomb blasts or thorium dioxide

Special concerns

Whether polycythemia vera, essential thrombocythemia, and agnogenic myeloid metaplasia progress to leukemia is influenced by the specific treatment strategies. Patients should be aware that some treatments, particularly radioactive phosphorus, can substantially increase the risk of developing cancer.

See also Acute myelocytic leukemia; Bone marrow aspiration and biopsy; Cytogenetic analysis; Cytology; Chromosome rearrangements; Hypercoagulation disorders; Myelosuppression; Radiation therapy; Ultrasonography.

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ORGANIZATIONS

MPD-Net Online Support Group from Myeloproliferative Diseases Research Center, Inc. 115 East 72nd Street, New York, NY 10021. <http://inform.acor.org/mpd/index.htm>.

The National Organization for Rare Disorders. P.O. Box 8923, New Fairfield, CT 06812-8923. (800) 999-6673. <http://www.rarediseases.org>.

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Myelosuppression

Description

Myelosuppression is a decrease in the production of blood cells. Normal blood contains large numbers of cells, including red blood cells to carry oxygen and white blood cells to fight infections. The blood also contains platelets, tiny cell fragments that initiate blood clotting. These cells and fragments are made in the bone marrow, a reddish substance found in the centers of some bones. Healthy bone marrow makes large numbers of red blood cells, white blood cells, and platelets each day to replace those that wear out. In myelosuppression, the bone marrow makes too few of these cells.

A decrease in the number of red blood cells, called **anemia**, is very common in cancer patients. A drop in white blood cell numbers is often a problem during **chemotherapy**. One type of white blood cell, called a neu-

KEY TERMS

Anemia—Too few red blood cells in the blood.

Blood cells—The red blood cells and white blood cells found in the blood.

Bone marrow—A group of cells and molecules found in the centers of some bones. It makes all of the cells found in the blood.

Erythropoietin—A growth factor that stimulates the bone marrow to make more red blood cells. It is also known as epoetin alfa.

Granulocyte colony-stimulating factor (G-CSF)—A growth factor that stimulates the bone marrow to make neutrophils and some other types of white blood cells. It is also known as filgrastim.

Granulocyte-macrophage colony-stimulating factor (GM-CSF)—A growth factor that stimulates the bone marrow to make neutrophils and some other types of white blood cells. It is also known as sargramostim or molgramostim.

Growth factor—A chemical that stimulates body cells to grow or make more cells. Growth factors are found naturally in the body, but can also be manufactured and used as drugs.

Interleukin 11 (IL-11)—A growth factor that stimulates the bone marrow to make platelets. It is also known as oprelvekin.

Neutropenia—Too few neutrophils in the blood.

Neutrophil—A type of white blood cell that destroys bacteria.

Packed red blood cells—Blood that has had the fluid portion (plasma) removed.

Platelets—Tiny fragments of cells that begin the blood clotting process. They are found in the blood.

Red blood cells—The cells in the blood that carry oxygen.

Thrombocytopenia—Too few platelets in the blood.

Transfusion—A transfer of blood or blood products from one person to another.

Transfusion reaction—An allergic reaction to some of the cells or proteins in another person's blood.

White blood cells—The cells in the blood that fight infections. There are several types of white blood cells.

trophil, is usually affected most severely. A decrease in these cells is called **neutropenia**. Because neutrophils are responsible for defending the body against bacteria, neutropenia increases the chance of an infection. **Thrombocytopenia**, a drop in the number of platelets in the blood, is more rare; platelet numbers become low enough to cause problems in less than 10% of cancer patients.

Myelosuppression is a painless condition, but the decreases in important blood cells can result in **fatigue**, an increased risk of infections, or excessive bleeding. The consequences vary from mild to life-threatening, depending on how low the blood cell numbers fall.

Causes

The most common cause of myelosuppression is cancer treatment. Many of the drugs used in chemotherapy temporarily suppress the bone marrow. Therapeutic x rays that reach the bone marrow are also destructive. Cancer cells can also cause myelosuppression. Some cancers invade the bone marrow and crowd out the cells normally found there. Others can suppress the bone marrow without invasion. Nutritional deficiencies, common in cancer patients, also slow blood cell production as do viruses and some non chemo drugs.

Myelosuppression usually starts seven to ten days after an injury to the bone marrow. However, the bone marrow generally returns to normal within the next few weeks. Less often, cumulative damage can be caused. Occasionally, irreversible damage causes permanent myelosuppression. Very intensive chemotherapy or radiation can destroy all of the cells in the bone marrow.

Treatments

Myelosuppression is not always treated, especially if it is mild.

If the myelosuppression is a result of chemotherapy or radiation therapy, the cancer treatments may be stopped, delayed, or reduced to give the bone marrow a chance to recover. This may mean that the full dose of the treatment is not received.

Careful monitoring of possible neutropenia in cancer patients is important. If a cancer patient has a fever

and other signs of possible infection, the physician may treat the patient with injected antibiotics, possibly for several days.

Red blood cells or platelets can be replaced by transfusions, packed red blood cells, or platelets. These treatments can be very effective in the short term; however, the transfused cells are short-lived and the treatment may need to be repeated. There is a small chance of a transfusion reaction and a slight risk of infection by a virus carried in the blood. Transfusions of white blood cells are ineffective and rarely given.

Injections of growth factors may also be effective. Growth factors are chemicals, found naturally in the body, that stimulate the bone marrow to make blood cells. Each type of growth factor affects specific blood cells. Several are being manufactured as drugs. They include **erythropoietin**, granulocyte colony-stimulating factor (G-CSF, or filgrastim), granulocyte-macrophage colony-stimulating factor (GM-CSF, or sargramostim), and interleukin 11 (**oprelvekin**). Erythropoietin injections stimulate red blood cell production. They can decrease the need for a transfusion and improve the quality of life. This drug has few side effects if the kidneys are healthy, but it may not be effective if the body is already making enough natural erythropoietin. G-CSF and GM-CSF can speed the return of neutrophils. Their side effects include **bone pain**, fevers, rashes, muscle pains, and nausea. Interleukin 11 can increase platelet numbers. Its side effects may include fluid retention, a rapid heartbeat, red eyes, and difficulty breathing. Growth factors are expensive and several injections are usually needed.

Complete destruction of the bone marrow is incompatible with life. If the bone marrow is severely damaged, a bone marrow transplant may be necessary.

Alternative and complementary therapies

Supportive therapy can help to minimize the effects of myelosuppression. If nutrition is a contributing factor, iron or vitamin supplements may be beneficial. **Antibiotics** can aid in preventing infections. Some patients find that mild exercise and enjoyable distractions help with fatigue.

See also Anemia; Bone marrow transplantation; Transfusion therapy.

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N

Nasal cancer

Definition

Nasal cancer is any cancer that occurs within the nose, either in the nasal vestibule (the immediate interior of the nose, just beyond the nostrils), or the nasal cavity (the deep interior of the nose). Many different types of cancer can occur within the nose, and the type of treatment and the chance of cure will vary according the type of cancer that occurs.

Description

Nasal cancers are very rare, making up less than 2% of all tumors of the respiratory tract in the United States. Less than 50 cases a year are diagnosed in the United States. Although squamous cell **carcinoma** is the most common type of cancer that occurs within the nose, many other types can also occur, including adenocarcinoma, **melanoma**, different kinds of **sarcomas**, inverted papilloma, **lymphoma**, and esthesioneuroblastoma.

Squamous cell carcinomas arise from skin tissue. They are the most common type and are often the result of either cigarette smoking or occupational exposure to dusts or chemical fumes. Adenocarcinomas are malignancies that resemble glandular tissue. Nasal adenocarcinomas are also often associated with occupational exposure to dusts or chemical fumes. T-cell lymphomas (Non-Hodgkins) in the nasal area are strongly associated with a virus (**Epstein-Barr virus**, EBV). Although nasal T-cell lymphomas are fairly common in some parts of the world, they are very rare in the United States.

Inverted papillomas are associated with another virus (**human papilloma virus**, HPV) and arise from benign but locally invasive nasal polyps. They are rare, comprising only about 0.5% of all nasal tumors. Although a definite association with HPV has been shown, a tumor may require interaction of the virus with chemicals or other factors, which appear to cause transformation of the inverted papilloma into squamous cell carcinoma in the nose. Esthesioneuroblastoma is a very rare nasal tumor, with less than 200 cases reported in the last 25 years. They are tumors that arise in the nerves in the nose, and have occurred most commonly in teenagers and senior citizens.

Demographics

Although the overall risk of nasal cancer is quite low (since this type of cancer is very rare), relative risks for some specific groups are fairly high. For example, nasal T-cell lymphomas are virus-associated and occur in high incidence in Asia and South America. Nasal squamous cell carcinomas occur much more frequently in cigarette smokers and individuals who have occupational exposures to dusts or chemical fumes, especially in Europe. Consumption of salted and pickled foods creates an increased relative risk of nasal cancer in Asia. Nasal cancers are also more frequent in some African populations that use mahogany wood in cooking fires.

In the United States, nasal cancers are rare. There are no significant racial differences in incidence. Males experience all types of nasal cancer in significantly greater numbers than women, probably due to more occupational exposure to agents that can cause these types of cancer. Most nasal cancers occur in people over 40, although the rare esthesioneuroblastoma has occurred in relatively high percentages in adolescents.

Causes and symptoms

All cancers are caused when a genetic mutation is made in a gene that is involved in the control of cell division. This mistake can arise naturally, can be inherited, or it can be caused by a virus, by sunlight or other radiation, or by some chemical that a person is exposed to, usually through eating, drinking or breathing. For nasal cancers, all of these factors have been shown to play a part.

The use of tobacco products has been strongly associated with the occurrence of nasal adenocarcinomas and squamous cell carcinomas. Chronic occupational

exposures to leather, wool, or wood dust or chemical mixtures, particularly nickel, dioxane, nitrosamine, chromium used in dye manufacturing, mustard gas, rubbing alcohol, or formaldehyde, have a demonstrated association with nasal adenocarcinomas and squamous cell carcinomas as well. Some rare nasal T-cell lymphomas have been shown to be very strongly associated with a virus (Epstein-Barr Virus, EBV). Some nasal malignancies (about 5%) begin as inverted papillomas, a locally aggressive tumor which does not usually metastasize but which may turn malignant. These are also thought to be caused by a virus, although a different one: Human papilloma virus (HPV). Some nasal cancers have a strong hereditary component: people with genetic alterations that cause hereditary **retinoblastoma** have a much higher incidence of nasal cancers than average, which indicates that the genetic change that caused their original disease may also contribute to nasal cancer.

People with nasal cancer may think that they have a cold or chronic sinus infections. They may experience a feeling of stuffiness or blockage in the nose, persistent nasal drainage, or frequent nose bleeds. Other symptoms can occur if the tumor has invaded other tissues around the nose, particularly the orbit of the eye or the base of the skull. Other symptoms which may occur include:

- double vision
- bulging of the eye
- a lump on the face or around the eye
- loose teeth
- frequent headaches

In advanced stages, patients with nasal cancers may suffer from **fatigue**, **weight loss**, lack of appetite (anorexia), and **fever**.

Diagnosis

When otherwise unexplainable symptoms lead a doctor to suspect that a patient may have nasal cancer, often he or she will arrange for endoscopic examination of the nasal cavity (and possibly the sinuses) in order to see if there is a tumor. Definite diagnosis requires a **biopsy**, in which a small piece of the tumor is cut out and examined to see what types of cells it contains. After a nasal cancer is diagnosed (depending on the type of cancer), many doctors will ask the patient to have an **x ray**, **computed tomography** scanning (CT scans), or **magnetic resonance imaging** (MRI). These techniques visualize the tumor and show the doctor how much the tumor has invaded surrounding tissues. Because treatment for nasal cancer, as well as **paranasal sinus cancer**, involves surgery in a small, complex space which requires the surgeon to set very precise surgical boundaries, and because most nasal cancers are advanced by the time a patient sees a doctor, it is very important that the doctor evaluate the tumor thoroughly before planning treatment. If the tumor appears to have invaded other tissues, often a doctor will schedule a surgical exploration of the tumor in order to better evaluate the cancer, with the goal of constructing the best possible treatment plan. Sometimes, in addition, surgical exploration is necessary to determine whether the position and invasion of the tumor into surrounding tissue makes surgical removal of the tumor impossible.

Treatment team

As the understanding of cancer grows and new treatment approaches are developed, the complexity of cancer treatment also increases. Today, a multidisciplinary approach to cancer treatment is considered necessary for effective patient care. People involved in the treatment of a nasal cancer will typically include the referring physician, an otolaryngologist, a medical oncologist, a pathologist, and a nurse. If **radiation therapy** is pursued, a radiation oncologist, radiation therapist, radiation nurse, radiation physicist, and a dosimetrist will also be involved. Treatment will also probably include a psychologist, nutritionist, social worker and chaplain. For nasal cancers, a reconstructive or plastic surgeon may be necessary for optimum cosmetic results after removal of a nasal tumor. If surgical removal of the eye is necessary, specialists in prosthetic eye replacement will be necessary as well.

Clinical staging, treatments, and prognosis

When a cancer develops, the original tumor can spread, usually through the blood or lymph system, to other parts of the body. Since the cancer spreads through the lymph system, often the lymph nodes in the area of the original tumor are the first other sites where cancerous cells can be found. Common other places that metastatic disease may appear are the lungs, the liver, and the bones.

One of the foremost goals of a doctor's assessment of a cancer patient is to determine how far the cancer has already spread and how likely it is to spread further, both of which are key factors in the likelihood that the patient will be cured. The assessment of the tumor's spread is termed staging, and the assessment of how aggressive the cancer cells are is termed grading.

Staging of nasal cancers is performed by visual inspection of tumors (maybe through endoscopy) or visualization of tumors by imaging techniques like x rays, MRIs, or CT scans. The doctor may also attempt to feel for tumors manually. This information will be

used to create an official stage for the tumor that is a standardized expression of how much the tumor has already spread.

Because tumors of the nasal vestibule and cavity are rare, and because they are comprised of so many different types, no one staging system has been defined for use with these cancers. Cancers of the paranasal sinuses have a defined staging system based on the TNM system, and this system is often used for describing nasal cancers. The T in the TNM system represents the growth of the local tumor, N describes the spread of the tumor to the lymph nodes, and M describes the spread, or **metastasis**, of the cancer to distant body sites. The cancer is given various numbered ratings in each letter category, and these are used to create a standardized stage. Generally, tumors with no invasion of local tissues are described as Stage I, while tumors with minimal invasion of local tissues are identified as Stage II. Tumors that have extensive local invasion or that have spread to the lymph nodes but which have not metastasized are described as Stage III or early Stage IV (A and B). Stage IVC tumors are any tumors which have metastasized.

Most nasal cancers (up to 80%) have already spread to other body sites by the time the symptoms prompt a patient to see their doctor. This fact, combined with the fact that the area is anatomically complex and tightly constructed, makes it very important that the first attempt at treatment is well-planned, with input from a multidisciplinary team and thorough evaluation of the cancer before treatment is begun.

Since cancers of the nasal cavity and vestibule include many different types of cancers, treatment will vary depending on the type of cancer involved, where it is located, and the extent to which it has already spread. Because of this, and because of the complexity of the anatomy in the area and the multitude of other important structures that may be involved in later stages, treatment of nasal cancers is highly individualized, with no firm standard practice guidelines.

For most nasal cancers, treatment will involve surgical removal of the tumor followed by four to five weeks of radiation therapy. In advanced cancers, preoperative radiation therapy may also be employed. However, since radiation therapy has proven very effective for nasal cancers and because radiation has better cosmetic results than surgical removal of a tumor, for many nasal cancers (especially T-cell lymphomas and esthesioneuroblastomas), radiation will be the initial treatment option. If the doctor decides to remove as much of the tumor as possible surgically, radiation therapy (external) will usually be used for four to five weeks after surgery in order to destroy any remaining cancerous tissue. One exception is the case of inverted papillomas, for which surgical excision alone is usually employed. Surgery, because of the tight anatomical area in which a surgeon must work, may also involve more recent techniques like cryosurgery (freezing tissue) or laser surgery.

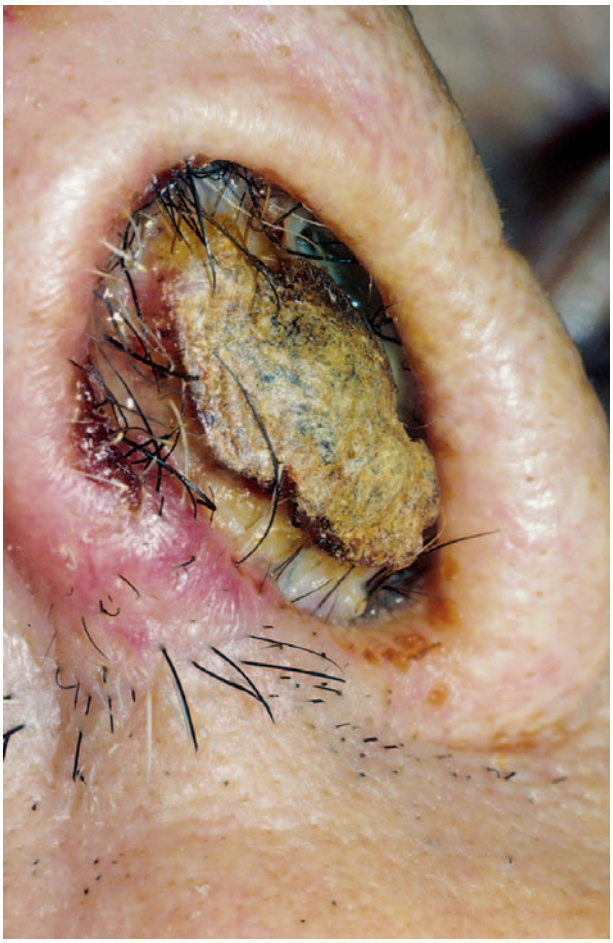
Tumors initially treated by either radiation or surgery alone may, if they come back, be treated by the untried option or by employing both. External radiation may be supplemented, especially in advanced nasal vestibule cancer, by internal radioactive implants. In addition, advanced stage or recurrent nasal cancer may be treated by **chemotherapy**, usually involving a combination of drugs. Drugs are used in combination in most chemotherapy because combinations of different drugs (with different side effects) deliver the highest cancer-destroying effect, while minimizing the chance for a serious adverse reaction to the therapy. The drug combinations used in nasal cancer vary on the type of cancer, and may include one or all of the drugs **cisplatin**, **fluorouracil**, **bleomycin**, or **methotrexate**. In addition, nasal cancers described as Stage III or IV will probably be treated with preventative radiation therapy of the neck area, in order to destroy cancerous cells which may have traveled to the lymph nodes.

Although nasal cancers are made up of many different types of cancer, all types of nasal cancers are considered aggressive. The majority of nasal cancers, because symptoms mimic upper respiratory illnesses and because symptoms often do not occur until the cancer has already filled up the nasal cavity and has invaded surrounding tissues, are already in advanced stages when a patient seeks medical help. For this reason, and because treatment is difficult because of the complexity of the anatomical area, fewer than half of nasal cancer patients survive. If the first treatment attempt is successful, and a patient is cancer-free at two years, however, chances improve greatly.

Nasal cancer is unusual in that, although many patients have metastasis to the lymph nodes or beyond (usually to the lungs), metastasis is not usually the reason for a patient's death. Most nasal cancer patients who succumb to the disease die from invasion of the tumor into vital areas of the brain.

Alternative and complementary therapies

Alternative and complementary therapies are treatments that are not traditional, first-line therapies like surgery, chemotherapy, and radiation. Complementary therapies are those that are meant to supplement traditional therapies and usually have the objective of relieving symptoms or helping cancer patients cope with the disease or traditional treatments. Alternative therapies



Cancerous tumor in nose. *(Custom Medical Stock Photo. Reproduced by permission.)*

are nontraditional treatments that are chosen instead of traditional treatments in an attempt to cure the disease. Alternative therapies have typically not been proven to be effective in the same way that traditional drugs are evaluated, in **clinical trials**.

Common complementary therapies that may be employed by patients with nasal cancer are art therapy, massage, meditation, visualization, music therapy, prayer, t'ai chi, and yoga or other forms of exercise, which reduce anxiety and can increase a patient's feeling of well-being.

Numerous alternative therapies exist in cancer treatment, but none has been proven in clinical trials to be effective. Laetril, a product of apricot seeds, is probably one of the most well known. Laetril contains a form of cyanide that may be released by tumor enzymes and may then act to kill cancerous cells. Laetril is not approved for use in the United States, although it is available in Mexico. The National Cancer Institute (NCI) sponsored two trials of Laetril in the late 1970s and early 1980s, but found Laetril to be ineffective and concluded that no further study of the substance was necessary. **Vitamins** and other nutritional elements like vitamins A, C, and E, and selenium are thought to act as **antioxidants**. Vitamin E, melatonin, aloe vera, and a compound called beta-1, 3-glucan are reported to stimulate the immune system. Natural substances like garlic, ginger, and shark cartilage are also commonly held to shrink tumors, with less defined modes of action.

Antineoplastons are believed by some to be another alternative approach to a cancer cure. Antineoplastons are small proteins which may act as molecular messengers and which may be absent from the urine and blood of many cancer patients. Proponents believe that replacing these proteins may have beneficial effects. The NCI has been unable to draw definitive conclusions about the usefulness of antineoplastons as a therapy because no large-scale clinical trials of the therapy have been completed.

Coping with cancer treatment

Treatment of nasal cancers commonly includes surgery, radiation therapy and chemotherapy. Although the use of chemotherapy and radiation therapy in addition to surgery has improved the chance of survival for nasal cancer patients, both of these treatments unavoidably result in damage to some healthy tissues and other undesirable side effects.

Fatigue is a very common side effect of both radiation therapy and chemotherapy. Side effects of the actual treatments combine with the natural depletion of the body's resources as it fights off the disease and normal psychological consequences of the disease such as **depression** to make coping with fatigue a very significant aspect of dealing with cancer treatment. The best way to deal with these symptoms is to cut back on stressful activities and take plenty of time to allow the body to heal. It is also important to try to maintain a well-balanced, nutritious diet, and to exercise. Patients should avoid as much extra stress as possible and should limit visitors, if needed, to avoid being overtired. At the same time, it is also important for psychological health for the patient to pursue their interests as much as possible and to avoid becoming isolated.

The biggest problem for those undergoing radiation therapy is the development of dry, sore, "burned" skin in the area being treated. (Radiation does not hurt during treatment and does not make the person radioactive.) Skin in the treatment area will become red, get itchy and sore, and may blister and peel, becoming painful. Patients with fair skin or those who have undergone previous chemotherapy have a greater risk of more serious

reactions. Dry, itchy or sore skin is temporary, but affected skin may be more sensitive to sun exposure for the rest of the patient's lifetime, so a good sunscreen and a hat should be used whenever affected skin is exposed to sunlight.

Other effects, specific to the nasal area, may also occur. Sometimes very thick mucus is produced that may be difficult to cough up. Some patients become hoarse and find it difficult to eat. It is important for patients to keep well-hydrated by drinking plenty of fluids and to eat as much protein as possible. If patients cannot eat enough to maintain a high-protein diet, liquid high-protein drinks should be consumed. Patients may be more susceptible to upper respiratory infections after treatment, so some physicians will prescribe preventative **antibiotics**. If eating is extremely painful, tylenol can be consumed in milk about thirty minutes before a meal for pain relief. Patients should be prepared for the fact that symptoms of radiation treatment can persist for up to a month after the last treatment.

Some of the more common side effects of chemotherapy include hair loss, and **nausea and vomiting**. Hair loss (**alopecia**) is a difficult part of dealing with cancer treatment for most patients, especially women. Hair may thin out gradually, or it may fall out in big clumps. To slow down the rate of hair loss, avoid any unnecessary sources of damage to the hair, like curling, blow-drying, or chemical treatments.

Different patients choose different ways of coping with the loss of their hair. Some patients may find they are more comfortable hiding hair loss with a wig; it is a good idea to cut off a lock of hair before hair loss begins in case a wig is later desired. Some patients may choose to remain bald, or may want to choose hats or scarves instead of wigs. In any case, it is important to remember that the loss of hair is a sign that the medication is doing its job, and that hair loss is temporary. Hair usually begins regrowth within a few months of the end of intensive chemotherapy, although it may come in a different color or texture than the original hair.

Nausea and vomiting are other fairly common side effects of many chemotherapy drugs. (Radiation to the brain or the GI tract can also cause nausea and vomiting.) After a few courses of chemotherapy drugs, some patients will become nauseated just from thinking about an upcoming treatment or from smelling certain odors. Drugs that combat nausea and vomiting can be prescribed, but are often not effective for anticipatory nausea. If nausea and vomiting are a problem, heavy, regular meals should be avoided in favor of small, frequent snacks made up of light but nourishing foods like soup. Avoiding food smells and other strong odors may help.

KEY TERMS

Carcinoma—Any malignant tumor

Endoscopy—A diagnostic procedure in which a miniature videocamera on the end of a flexible tube is inserted into internal body cavities so that the physician can view the internal structures.

Lymphoma—A type of cancer that arises in the lymph nodes

Nasal polyp—A non-cancerous mass that grows out from the inner lining of the nasal cavity

Sarcoma—A tumor that arises from bone or connective tissue

Squamous cell carcinoma—A malignancy that arises from outer skin cells

Desensitization, hypnosis, guided imagery, and relaxation techniques may be used if nausea and vomiting are severe. These techniques help to identify the triggers for the nausea and vomiting, decrease patient anxiety, and distract the patient from thinking about getting sick. Acupressure bands, commonly used for seasickness, and acupuncture, may also provide some relief for some patients.

Both radiation therapy and chemotherapy treatments require a substantial level of commitment from the patient in terms of time and emotional energy. Fear and anxiety are major factors in coping with cancer in general and these cancer treatments. The feelings are completely normal. Some patients find that concentrating on restful, pleasurable activities like hobbies, prayer, or meditation is helpful in decreasing negative emotions. It is also very important that patients have people to whom they can express their fears and other negative emotions. Support groups may help to provide an environment where fears can be freely expressed and understood.

Clinical trials

Clinical trials are studies in which new treatments for disease are evaluated in human patients. Current clinical trials for nasal cancer patients are concentrating on the addition of chemotherapy to the more common treatments of surgery and radiation therapy, either before or after those treatments, in order to improve cure rates or to lessen the side effects of radiation.

Nasal cancer patients are also being recruited for a clinical trial evaluating an alternative therapy known as antineoplaston therapy.

Prevention

Although mutations in genetic material happen frequently, most of these do not result in cancer. This is because a healthy body repairs most mistakes before a cancer develops and because, if a cancer does develop, the immune system of a healthy body will usually destroy it. In general, therefore, a healthy lifestyle that includes exercise, plenty of sleep, a diet rich in fruits and vegetables, regular health screenings and the avoidance of stress, excessive sun exposure, tobacco use, or excessive **alcohol consumption** will help to prevent most cancers.

Since nasal cancers, in particular, are often caused by chemical exposures, many of these cancers are preventable by avoiding excessive inhalation of wood dust or chemical mixtures and by avoiding use of all tobacco products. (Nasal cancers resulting from wood dust appear to require high-dose, long-term exposure, especially to hardwoods.)

One type of nasal cancer appears to be virus-associated and is more prevalent in people with a history of nasal polyps. People who are diagnosed with nasal polyps should discuss their removal with their physicians and have existing polyps checked regularly in order to detect a malignant polyp as quickly as possible.

Patients with nasal cancer can increase their chances of a cure by making sure that they see their doctors for all scheduled follow-up appointments. This is especially important for the first two years (when most recurrences of nasal cancer occur), but it is also important to maintain follow-up beyond that. Many nasal cancer patients experience a second tumor somewhere else in the upper respiratory tract.

Special concerns

One of the unique aspects of dealing with nasal cancer is the fact that surgical removal of a nasal tumor can result in substantial facial disfigurement. Patients who are dealing with this aspect of nasal cancer are forced to cope with the substantial emotional burden of disfigurement in addition to the other emotional ramifications of the disease.

People with facial disfigurement may be forced to cope with negative reactions from other people in public places, including staring, whispering, rude remarks or averted eyes, and other avoidance of interpersonal interaction.

In addition, the loss of the accustomed appearance will be experienced much like a bereavement. Patients will probably initially feel numb, then experience intense, overwhelming feelings of sadness, fear, and anger. The period characterized by intense, almost unbearable emotions is usually followed by a period of time when the patient feels completely empty, fatigued, and apathetic. Given time, most patients will come to an acceptance of their new reality and begin to enjoy old friends and activities again. It is important not to expect patients in such circumstances to immediately accept their situation or to suppress the natural emotions that accompany the change in their appearance. Patients can ease the process by trying to focus on one day at a time and by finding people who can help them work through the process by listening and accepting their emotions. It is very important that a patient dealing with these changes have friends or family members to whom they can express their feelings of grief and anger. A support group might also be helpful.

QUESTIONS TO ASK THE DOCTOR

- Can you explain what kind of cancer I have?
- Can you explain the grade and stage of my cancer? What are the chances that it will come back?
- How was this cancer diagnosed?
- What is my prognosis?
- How much will the surgery alter my facial appearance?
- What treatments are we going to pursue? What happens if these don't work?
- Do you have experience in treating this type of cancer?
- Is there anything I can do to optimize treatment? Are there any particular side effects I should expect?
- Are there complementary therapies that you would recommend? Any other things that would help me cope with the diagnosis or treatment?
- How often will I need further check-ups? Is there anything I can do to keep this cancer from coming back?

See also Cryotherapy; Tumor grading; Tumor staging.

Resources

BOOKS

Buckman, R. *What You Really Need to Know About Cancer*. Baltimore: Johns Hopkins University Press, 1999.

ORGANIZATIONS

American Cancer Society, 1599 Clifton Road, NE, Atlanta, GA 30329-4251. (800)586–4872 <http://www.cancer.org>.

National Cancer Institute, 9000 Rockville Pike, Bethesda, Maryland, 20892. (800)422–6237. <http:www.nci.nih.gov>.

The Wellness Community, 10921 Reed Harman Highway, Cincinnati, Ohio, 45242 (888)793–9355. <http://www.wellness-community.org>.

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Nasopharyngeal cancer

Definition

Nasopharyngeal cancer is an uncontrolled growth of cells that begins in the nasopharynx, the passageway at the back of the nose.

Description

The nasopharynx connects the nose (hence, naso) to the pharynx, the shared passageway for air and food at the back of the nose and mouth. Air moves through the pharynx on its way into and out of the trachea, the tube that carries air to the lungs. Food passes through the pharynx on its way to the esophagus, the muscular tube that carries food to the stomach.

Although it is possible for people to breathe through the mouth, breathing through the nose is better. The nose warms and moistens air, and the interior of the nose has hairs to filter particles from the air. Thus, any blockage, such as a tumor or cancer in the nasopharynx, interferes with normal breathing.

Not all tumors that grow in the nasopharynx are malignant. Many are benign, but the tumors still cause problems because they often grow into the vessels that supply blood to the nose. Malignant cancers in the nasopharynx grow from squamous, or flat, epithelial cells. Epithelial cells form body coverings, such as skin. Cancers that originate in epithelial cells are known as carcinomas.

Demographics

Nasopharyngeal cancer is rare in most parts of the world. The exception is in Southeast Asia, where there are as many as 40 new cases each year for every 100,000 people. In other parts of the world, there are as few as one new case per year for every 100,000 people. Men are at a greater risk than women. Although all age groups can be affected by this cancer, like many other cancers, people over the age of 40 tend to be more susceptible.

Causes and symptoms

Several factors put people at risk for nasopharyngeal cancer. One is an infection with a type of herpes virus called **Epstein-Barr virus** (EBV). Another factor is genetic make-up, or inherited DNA. Finally, anything that introduces radioactive elements into the diet or respiratory pathway increases the risk of developing this cancer.

In certain parts of China, the soil has a high concentration of uranium and thorium, which break down into radioactive elements such as radium and radon. The elements are taken up by trees, which are burned for wood and become airborne. They also dissolve in water, and fish and plants draw them up. The fish are eaten. Some of the plants are used for tea. The scenario seems to increase the risk of nasopharyngeal cancer, but the exact way in which it does is not known.

In all parts of the world, people who work in sawmills or with wood products have a higher likelihood of acquiring nasopharyngeal cancer. Sawdust or chemicals in the wood may contribute to its development.

Recently, E. Lopez-Lizarraga demonstrated that human papilloma virus (HPV) is often present in people who contract nasopharyngeal cancer. Neither this link nor the others cited show a precise cause and effect, however. Some of the links may mask true causes. For example, in the HPV study, subjects who had HPV infection also tended to have poor oral hygiene. And in the case of EBV, infection with the virus is so common that some researchers are now investigating whether there is a unique strain of the EBV that puts individuals at greater risk for nasopharyngeal cancer.

Symptoms of nasopharyngeal cancer include:

- lump in the nose or neck
- headaches
- ear pain
- numbness on the side of the face
- difficulty breathing
- difficulty speaking

Diagnosis

A physician examines the nasopharynx in various ways, usually starting with an instrument such as a

nasoscope. The nasoscope allows a look at the inside of the nasal cavity. Palpating, or touching, lymph nodes in the neck to check for enlarged ones is also part of the examination.

If suspicious growths are found, a **biopsy** is done to take a tissue sample. Different types of biopsy can be used. An incision may be made to obtain tissue, or a needle with a small diameter may be inserted into a suspicious mass to obtain cells, especially if there is a lump in the neck.

Computed tomography (CT) and **magnetic resonance imaging** (MRI) scans are also used. They help determine whether the cancer has spread from the walls of the nasopharynx. MRI offers a good way to examine the tonsils and the back of the tongue, which are soft tissues. CT is used as a way of studying the jaw, which is bone.

Treatment team

Generally, physicians with special training in the organs of the nose and throat take initial responsibility for the care of a patient with nasopharyngeal cancer. They are called otolaryngologists, or occasionally, otorhinolaryngologists. Otolaryngologists are usually labeled ENT (for ear, nose, and throat) specialists. An ENT specializing in cancer will probably lead the team, accompanied by radiation therapists and oncologists.

Clinical staging, treatments, and prognosis

Stage I describes a cancer that has not spread. It is not in the lymph nodes and is localized in the nasopharynx. Stage II describes a larger cancer, one that affects more than half the area of the nasopharynx, that is not in the lymph nodes. Stage III nasopharyngeal cancer has spread beyond the nasopharynx; it might affect the oropharynx, the cavity at the back of the mouth, or part of the throat. Or, it might have spread to the lymph nodes. Stage IV involves one or more of the following indications:

- spread of cancer to a site near the original site, such as the bones and nerves of the head
- more than one lymph node with cancer
- spread to other parts of the body, such as the larynx, the trachea, the bronchi, the esophagus, or more distant points, such as the lungs

The outlook for recovery from nasopharyngeal cancer is better the earlier the stage in which the cancer is diagnosed. For stage I and stage II, radiation or **chemotherapy** treatment of the affected area is sometimes all that is required to halt the cell growth. Decisions about which method to use depend on many factors, but the tolerance a patient has for radiation or chemotherapy and the size of the tumor are important.

Often, the most promising treatment option for a person with nasopharyngeal cancer is a clinical trial. The outlook for early stage diagnoses of nasopharyngeal cancer is good. The five-year survival rate is over 80% for small cancers, which are typically in Stage I. Cancers that are larger, but have not spread to the lymph nodes, usually have survival rate of 50% or more. Unfortunately, about half of all people diagnosed with nasopharyngeal cancer are not diagnosed until the cancer is advanced, which leads to a poorer prognosis.

Coping with cancer treatment

The patient should be an active member of the treatment team, listening to information and making decisions about which course of treatment to take. Premier cancer centers encourage such a role.

Appetite might be affected before, during, and after treatment. Before treatment, the presence of a tumor can interfere with chewing and swallowing food, and food might not seem as appealing as it once did. During treatment, particularly radiation treatment, the treated nasopharynx will be sore, and eating and breathing may be difficult.

Patients should also seek out a support network to help them cope with the psychological implications of cancer. In addition to family and friends, local support organizations can offer guidance, answer questions, and link newly diagnosed patients with others who have survived a similar experience.

KEY TERMS

Biopsy—A diagnostic procedure in which a tissue sample is removed from the body for examination.

Computed tomography (CT)—A radiographic technique in which multiple x-ray images assembled by a computer to give a three-dimensional image of a structure.

Endoscope—Instrument designed to allow direct visual inspection of body cavities, a sort of microscope in a long access tube.

Magnetic resonance imaging (MRI)—Magnetic fields and radio frequency waves are used to image internal structures of the body.

Nasoscope—A type of endoscope designed specifically to be inserted through the nose and used for examination of the nasal cavity.

QUESTIONS TO ASK THE DOCTOR

- In what stage is this cancer?
- What is the outlook for a patient with my profile?
- What are the side effects of the treatments that are recommended? Which treatment gives the best combination of survival and quality of life?
- Is there a clinical trial for which I am eligible?

Alternative and complementary therapies

Any technique, such as yoga, meditation, or biofeedback, that helps a patient cope with anxiety over the condition and discomfort from treatment is useful and should be explored as an option. Many herbal remedies are available to ease the symptoms of nausea that accompany treatment; the physician, however, should be notified of any remedies, herbal or otherwise, that are taken.

Clinical trials

There are a number of **clinical trials** currently in progress, especially with biological response modifiers (BMR), or substances that take advantage of the capabilities of the body's own immune system. **Aldesleukin** is one BMR that has been used to fight nasopharyngeal cancer, with inconclusive results. The Cancer Information Service at the National Institutes of Health offers information about clinical trials that are looking for volunteers. The service offers a toll-free number at (800) 422-6237.

Prevention

The link between HPV and nasopharyngeal cancer suggests that any precaution taken to avoid contracting sexually transmitted diseases, such as the use of condoms, affords protection. Radon gas levels should be checked in homes, and measures taken to reduce them if they are high. Individuals working with wood, especially those exposed to sawdust and chemicals, should wear protective respiratory covers, such as a breathing mask.

Special concerns

Additional cancers that begin in the nasopharynx can start in the lymph cells found there. Because of their origin, these cancers are called lymphomas.

See also Oral cancer; Oropharyngeal cancer.

Resources

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ORGANIZATIONS

SPOHNC, Support for People with Oral and Head and Neck Cancer. P.O. Box 53, Locust Valley, NY 11560-0053. (800) 377–0928. <http://www.spohnc.org>.

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Nausea and vomiting

Description

Nausea and vomiting are recognized as two separate and distinct conditions. Nausea is the subjective, unpleasant feeling or urge to vomit, which may or may not result in vomiting. Vomiting is the forceful expelling of the contents of the stomach and intestines through the mouth. To some, nausea is a more distressing symptom than vomiting. Nausea and vomiting are major problems for patients being treated with cancer, with approximately 50% of patients experiencing nausea and vomiting as a result of cancer treatments even though **antiemetics** (anti-nausea and vomiting medications) were used. In addition, more than 50% of cancer patients experience nausea and vomiting as a result of progression of the disease, or as a result of exposure to other therapies used to treat the cancer.

Not all patients diagnosed with cancer will experience nausea and vomiting. However, nausea and vomiting remain two of the side effects associated with cancer and cancer treatment that patients and their families fear the most. The negative aspects of nausea and vomiting can influence all facets of a patient's life. If nausea and vomiting are not controlled in the patient with cancer, the result can be serious metabolic problems such as disturbances in fluid and electrolyte balance and nutritional status. Psychological problems associated with nausea and vomiting include anxiety and **depression**. Uncontrolled nausea and vomiting can also lead to the decision by the patient to stop potentially curative cancer therapy.

Causes

The most common causes of nausea and vomiting in cancer patients include treatment with **chemotherapy** and **radiation therapy**; tumor spread to the gastrointestinal tract, liver, and brain; constipation; infection; and use of some **opioids**, which are drugs used to treat cancer pain. The mechanisms that control nausea and vomiting are not fully understood, but both are controlled by the central nervous system. Nausea is thought to arise from stimulation of the autonomic nervous system. It is theorized that chemotherapy causes vomiting by stimulating areas in the gastrointestinal tract and the brain. The areas in the brain that are stimulated are the chemoreceptor trigger zone (CTZ) and the emetic or vomiting center (VC). When the VC is stimulated, muscular contractions of the abdomen, chest wall, and diaphragm occur, which result in the expulsion of stomach and intestinal contents.

Chemotherapy-induced nausea and vomiting

Not all chemotherapeutic agents cause nausea and vomiting. Chemotherapy drugs vary in their ability or potential to cause nausea and vomiting. This variation is known as the emetogenic potential of the drug, or the potential of the drug to cause emesis. Chemotherapy drugs are classified as having severe (greater than 90% of patients exposed to this drug will experience nausea and vomiting), high (60–90% of patients will experience nausea and vomiting), moderate (30–60% will experience nausea and vomiting), low (10–30% will experience nausea and vomiting), and very low (less than 10% experience nausea and vomiting) emetogenic potential.

The incidence and severity of chemotherapy-induced nausea and vomiting varies and is related to the following factors: the emetogenic potential of the drug, the drug dosage, the schedule of administration of the drug, and the route of the drug. For example, even a drug with a low emetogenic potential may cause nausea and vomiting if given at higher doses. Factors that are associated with increased nausea and vomiting after chemotherapy include female gender, age greater than six in children, age less than 50 in adults, history of motion sickness, and history of vomiting in pregnancy.

When nausea and vomiting result from chemotherapy administration, the nausea and vomiting can be classified as anticipatory, acute, or delayed. Anticipatory nausea and vomiting occur prior to the actual chemotherapy treatment and are a response primarily to an environmental stimulus, such as a specific odor, which is then associated with the chemotherapy treatment in the future. That is, the smell of the odor alone can be enough to induce or trigger nausea and vomiting in the sensitized patient. Acute nausea and vomiting occur within 24 hours of administration of the chemotherapeutic agent. Delayed nausea and vomiting occur after the acute phase and may last 48 or more hours after chemotherapy administration.

Radiation therapy induced nausea and vomiting

Although not all patients receiving radiation therapy will experience nausea and vomiting, patients receiving radiation therapy to the gastrointestinal tract and brain are most likely to experience those side effects. Radiation therapy to the brain is believed to stimulate the CTZ, the VC, or both. The higher the radiation therapy dose and the greater the body surface area irradiated, the higher the potential for nausea and vomiting. Also, the larger the amount of gastrointestinal tract tissue exposed to radiation the more likely nausea and vomiting will occur. Nausea and vomiting associated with radiation therapy usually occurs one-half hour to several hours after treatment and usually does not occur on the days when the patient is not undergoing treatment.

Treatments

Pharmacologic management

The most commonly used intervention to manage nausea and vomiting in cancer patients is the use of antiemetic drugs. Many of these drugs work by inhibiting stimulation of the CTZ and perhaps the VC. Most of the drugs used today to clinically treat nausea and vomiting are classified into one of the following groups: dopaminergic antagonists, neurokinin receptor antagonists, **corticosteroids**, cannabinoids, and serotonin receptor antagonists. Antiemetics can be utilized as single agents or several drugs can be prescribed together as combination therapy.

Examples of dopaminergic antagonists include phenothiazines such as prochlorperazine (Compazine), substituted benzamides such as metaclopramide (Reglan), and butyrophenones such as droperidol (Inapsine) and haloperidol (Haldol). Side effects of the dopaminergic antagonists include extrapyramidal reactions (e.g., tremors, slurred speech, anxiety, distress, paranoia) and sedation. In 2004, the FDA approved a new drug called aprepitant (Emend) for use in cancer patients. It is used in combination with other antiemetics for relief of acute and delayed nausea and vomiting caused by high-dose chemotherapy, most often caused by the chemotherapy drug cisplatin. Side effects of aprepitant include fatigue, dizziness, stomach pain, nausea, hiccups, diarrhea, constipation, and loss of appetite.

Steroids may be used to treat mild to moderately emetogenic chemotherapy. However, long-term corticosteroid use is considered inappropriate due to the multiple adverse effects associated with long-term use.

Cannabinoids (substances similar to, or derived from, **marijuana**) may be effective in selected patients but are usually not prescribed as first line therapy due to generally low rates of effectiveness. Controversy continues to exist related to the use of cannabinoids, which may not be accepted cultural or societal practice for some patients. Side effects of cannabinoids include physical and psychogenic effects such as acute withdrawal syndrome, dizziness, dry mouth, sedation, depression, anxiety, paranoia, and panic.

The newest class of antiemetics is the serotonin or 5-HT_3 antagonists. In 2001, three serotonin receptor antagonists were available in the United States: granisetron (Kytril), ondansetron (Zofran), and dolasetron (Anzemet). Serotonin receptor antagonists are better tolerated, are generally more effective, and result in fewer side effects than previously available antiemetics. A common adverse effect of the serotonin antagonists is asthenia, a state of unusual fatigue and weakness. Asthenia usually occurs two to three days after treatment with serotonin antagonists and may last one to four days. Serotonin receptor antagonists may not be offered or made available to all patients due to the relatively high cost of the drugs. Controversy exists related to the optimal role of serotonin receptor antagonists. Some clinicians argue there is the potential for overuse of the serotonin receptor antagonists when used to treat patients who are not receiving chemotherapeutic agents with moderate to severe emetogenic potential and when less expensive agents would be as effective.

Another class of drugs, the benzodiazepines including **lorazepam** (Ativan), midazolam (Versed), and alprazolam (Xanax), may be used in conjunction with antiemetics in the prevention and treatment of anxiety and expected chemotherapy-induced nausea and vomiting. These agents appear to be especially effective in highly emetogenic regimens administered to children. The benzodiazepines have only modest antiemetic properties. Therefore, they are usually used as adjuncts to antiemetic agents. Adverse effects of the benzodiazepines include sedation, confusion, hypotension (unusually low blood pressure), and visual disturbances.

Alternative and complementary therapies

The use of antiemetics is considered the cornerstone of therapy to treat chemotherapy-induced vomiting. Nonpharmacologic therapies may be used in conjunction with pharmacologic agents to enhance the effects of the drugs. Nonpharmacologic strategies include behavioral interventions such as guided imagery, hypnosis, systematic desensitization, and attentional distraction. Dietary interventions such as eating cold or room temperature foods and foods with minimal odors while avoiding spicy, salty, sweet, or high-fat foods may be beneficial to some patients while undergoing chemotherapy treatments. Another dietary recommendation is the use of ginger or ginger capsules to decrease episodes of nausea and vomiting. Acupressure, specifically stimulation of the Nei-Guan point (P6) of the dominant arm or stimulation of the Inner Gate and ST36 or Three Miles point (below the knee and lateral—outside area—to the tibia) has proven helpful to some patients. Music therapy interventions have also been effective as diversional interventions to reduce incidence and severity of chemotherapy-induced nausea and vomiting.

KEY TERMS

Antiemetics—Medications used to treat nausea and vomiting.

Emesis—An act or episode of vomiting.

Retching—Dry heaves that sometimes accompany nausea and vomiting.

Vomiting center—The location in the medulla of the brain that when stimulated leads to emesis.

Resources

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Navelbine *see* **Vinorelbine**

Nephrostomy

Definition

Nephrostomy is a procedure in which a catheter (plastic tube) is inserted through the skin and into the kidney to drain it of urine. Urine drains into a bag outside the body.

Purpose

The ureter is the tube that carries urine from the kidney to the bladder. When this tube is blocked, urine backs up into the kidney. Serious, irreversible kidney damage can occur because of this backflow of urine. Infection is also a common implication in this stagnant urine.

Nephrostomy is performed in several different circumstances:

- when the ureter is blocked by a kidney stone
- when the ureter is blocked by a tumor
- when there is a hole in the ureter or bladder and urine is leaking into the body
- as a diagnostic procedure to assess kidney anatomy
- as a diagnostic procedure to assess kidney function

Precautions

People preparing for a nephrostomy should review with their doctors all the medications they are taking. People taking anticoagulants (blood thinners such as Coumadin) may need to stop medication. People taking metformin (Glucophage) may need to stop taking the medication for several days before and after nephrostomy. Diabetics should discuss modifying their insulin doses because fasting is required before the procedure.

Description

Nephrostomy is done by an interventional radiologist or urologist with special training in the procedure. It can be done either as an inpatient or an outpatient procedure, depending on why it is needed. For most cancer patients, nephrostomy is an inpatient procedure that is covered by insurance.

First, the patient is given an anesthetic to numb the area where the catheter will be inserted. The doctor then inserts a needle into the kidney. There are several imaging technologies such as ultrasound and **computed tomography** that are used to help the doctor guide the needle into the correct place.

QUESTIONS TO ASK THE DOCTOR

- Why am I having a nephrostomy?
- How long do you think I will have to stay in the hospital?
- How long do you expect the catheter to stay in?
- How much help will I need in caring for the catheter?

Next, a fine guide wire follows the needle. The catheter, which is about the same diameter as IV tubing, follows the guide wire to its proper location. The catheter is then connected to a bag outside the body that collects the urine. The catheter and bag are secured so that the catheter will not pull out. The procedure usually takes one to two hours.

Preparation

Either the day before or on the day of the nephrostomy, blood samples will be taken. Other diagnostic tests done before the procedure vary depending on why the nephrostomy is being done, but the patient may have a computed tomography (CT) scan or ultrasound to help the doctor locate the blockage.

Patients should not eat for eight hours before a nephrostomy. On the day of the procedure, the patient will have an intravenous (IV) line placed in a vein in the arm. Through this the patient will receive **antibiotics** to prevent infection, medication for pain, and fluids. The IV line will remain in place after the procedure for at least several hours, and often longer.

Aftercare

Outpatients will be expected to stay about 8–12 hours after the procedure to make sure the catheter is functioning properly. They should plan to have someone drive them home and stay with them at least the first 24 hours after the procedure. Inpatients may stay in the hospital several days. Generally people feel sore where the catheter is inserted for about a week to ten days.

Care of the catheter is important. The catheter will be located on the patient's back, so it may be necessary to have someone help with catheter care. The catheter should be kept dry and protected from water when taking showers. The skin around it should be kept clean, and the dressing over the area changed frequently. Special care is needed in handling the urine collection bag so that it does not dislodge the catheter.

Risks

Nephrostomy is an established and generally safe procedure. As with all operations, there is always a risk of allergic reaction to anesthesia, bleeding, and infection.

Normal results

In a successful nephrostomy, the catheter is inserted, and urine drains into the collection bag. How long the catheter stays in place depends on the reason for its insertion. In people with pelvic cancer or **bladder cancer** where the ureter is blocked by a tumor, the catheter will stay in place until the tumor is surgically removed. If the cancer is inoperable, the catheter may have to stay in place for the rest of the patient's life.

Abnormal results

Bruising at the catheter insertion site occurs in about half of people who have a nephrostomy. This is a minor complication. Major complications are infrequent, but include the tube becoming blocked or dislodged requiring tube replacement, bleeding and blood in the urine, and perforation of other organs.

Resources

OTHER

American Cancer Society. National Headquarters, 1599 Clifton Road NE, Atlanta, GA 30329. 800–ACS–2345. <http://www.cancer.org>.

Cancer Information Service. National Cancer Institute, Building 31, Room 10A19, 9000 Rockville Pike, Bethesda, MD 20892. –800–4–CANCER. <http://www.nci.nih.gov/cancerinfo/index.html>.

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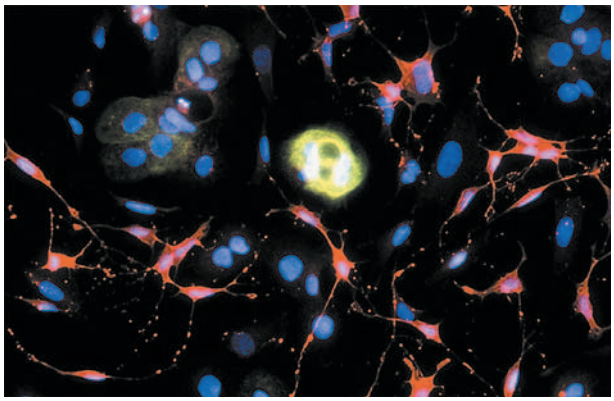
Tish Davidson, A.M.

Neuroblastoma

Definition

Neuroblastoma is a type of cancer that usually originates either in the tissues of the adrenal gland or in the ganglia of the abdomen or in the ganglia of the nervous system. (Ganglia are masses of nerve tissue or groups of nerve cells.) Tumors develop in the nerve tissue in the neck, chest, abdomen, or pelvis.



Immunofluorescent light micrograph of human neuroblastoma cancer cells. The normal epithelial cells appear green, the cytoplasm of neuroblastoma is red, and the nuclei are blue. *(Photograph by Nancy Kedersha. Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Description

Neuroblastoma is one of the few cancer types known to secrete hormones. It occurs most often in children, and it is the third most common cancer that occurs in children. Approximately 7.5% of the **childhood cancers** diagnosed in 2001 were neuroblastomas, affecting one in 80,000 to 100,000 children in the United States. Close to 50% of cases of neuroblastoma occur in children younger than two years old. The disease is sometimes present at birth, but is usually not noticed until later. By the time the disease is diagnosed, it has often spread to the lymph nodes, liver, lungs, bones, or bone marrow. Approximately one-third of neuroblastomas start in the adrenal glands.

Demographics

According to some reports, African-American children develop the disease at a slightly higher rate than Caucasian children (8.7 per million compared to 8.0 per million cases diagnosed).

Causes and symptoms

The causes of neuroblastoma are not precisely known. Current research holds that neuroblastomas develop when cells produced by the fetus (neuroblast cells) fail to mature into normal nerve or adrenal cells and keep growing and proliferating. The first symptom of a neuroblastoma is usually an unusual growth or lump, found in most cases in the abdomen of the child,

causing discomfort or a sensation of fullness and pain. Other symptoms such as numbness and **fatigue**, arise because of pressure caused by the tumor. **Bone pain** also occurs if the cancer has spread to the bone. If it has spread to the area behind the eye, the cancer may cause protruding eyes and dark circles around the eyes; in a few cases, blindness may be the presenting symptom. Or paralysis may result from compression of the spinal cord. **Fever** is also reported in one case out of four. High blood pressure, persistent **diarrhea**, rapid heartbeat, reddening of the skin, and sweating occur occasionally. Some children may also have uncoordinated or jerky muscle movements, or uncontrollable eye movements, but these symptoms are rare. If the disease spreads to the skin, blue or purple patches are observed.

Diagnosis

A diagnosis of neuroblastoma usually requires blood and urine tests to investigate the nature and quantity of chemicals (neurotransmitters) released by the nerve cells. These are broken down by the body and released in urine. Additionally, scanning techniques are used to confirm the diagnosis of neuroblastoma. These techniques produce images or pictures of the inside of the body and they include **computed tomography** scan (CT scan) and **magnetic resonance imaging** (MRI). To confirm the diagnosis, the physician will surgically remove some of the tissue from the tumor or bone marrow (**biopsy**), and examine the cells under the microscope.

Treatment team

The treatment team usually consists of an oncologist specialized in the treatment of neuroblastoma, a surgeon to perform biopsies and possibly attempt surgical removal of the tumor, a **radiation therapy** team and, if indicated, a **bone marrow transplantation** team.

Clinical staging, treatments, and prognosis

Staging

Once neuroblastoma has been diagnosed, the physician will perform more tests to determine if the cancer has spread to other tissues in the body. This process, called staging, is important for the physician to determine how to treat the cancer and check liver and kidney function. The staging system for neuroblastoma is based on how far the disease has spread from its original site to other tissues in the body.

Localized resectable (able to be cut out) neuroblastoma is confined to the site of origin, with no evidence that it has spread to other tissues, and the cancer can be surgically removed. Localized unresectable

KEY TERMS

Adjuvant chemotherapy—Treatment of the tumor with drugs after surgery to kill as many of the remaining cancer cells as possible.

Adrenal gland—Gland located above each kidney consisting of an outer wall (cortex) that produces steroid hormones and an inner section (medulla) that produces other important hormones, such as adrenaline and noradrenaline.

Alternative therapy—A therapy is generally called alternative when it is used instead of conventional cancer treatments.

Biopsy—A small sample of tissue removed from the site of the tumor to be examined under a microscope.

Complementary therapy—A therapy is called complementary when it is used in addition to conventional cancer treatments.

Conventional therapy—Treatments that are widely accepted and practiced by the mainstream medical community.

Disseminated—Spread to other tissues.

Hormone—A substance produced by specialized cells that affects the way the body carries out the biochemical and energy-producing processes required to maintain health (metabolism).

Localized—Confined to a small area.

Monoclonal antibody—A protein substance which is produced in the laboratory by a single population of cells. They are being tested as a possible form of cancer treatment.

Neoadjuvant chemotherapy—Treatment of the tumor with drugs before surgery to reduce the size of the tumor.

Neuroblast cells—Cells produced by the fetus which mature into nerve cells and adrenal medulla cells.

Resectable cancer—A tumor that can be surgically removed.

Salvage therapy—Treatment measures taken late in the course of a disease after other therapies have failed. It is also known as rescue therapy.

Staging system—A system based on how far the cancer has spread from its original site, developed to help the physician determine how best to treat the disease.

Unresectable cancer—A tumor that cannot be completely removed by surgery.

neuroblastoma is confined to the site of origin, but the cancer cannot be completely removed surgically. Regional neuroblastoma has extended beyond its original site, to regional lymph nodes, and/or surrounding organs or tissues, but has not spread to distant sites in the body. Disseminated neuroblastoma has spread to distant lymph nodes, bone, liver, skin, bone marrow, and/or other organs. Stage 4S (or IVS, or "special") neuroblastoma has spread only to liver, skin, and/or, to a very limited extent, bone marrow. Recurrent neuroblastoma means that the cancer has come back, or continued to spread after it has been treated. It may come back in the original site or in another part of the body.

Treatments

Treatments are available for children with all stages of neuroblastoma. More than one of these treatments may be used, depending on the stage of the disease. The four types of treatment used are:

- Surgery (removing the tumor in an operation)
- Radiation therapy (using high-energy x rays to kill cancer cells)
- **Chemotherapy** (using drugs to kill cancer cells)
- Bone marrow transplantation (replacing the patient's bone marrow cells with those from a healthy person).

Surgery is used whenever possible, to remove as much of the cancer as possible, and can generally cure the disease if the cancer has not spread to other areas of the body. Before surgery, chemotherapy may be used to shrink the tumor so that it can be more easily removed during surgery; this is called neoadjuvant chemotherapy. Radiation therapy is often used after surgery; high-energy rays (radiation) are used to kill as many of the remaining cancer cells as possible. Chemotherapy (called adjuvant chemotherapy) may also be used after surgery to kill remaining cells. Bone marrow transplantation is used to replace bone marrow cells killed by radiation or chemotherapy. In some cases the patient's own bone marrow is removed prior to treatment and saved for transplantation later. Other times the bone marrow comes from a matched donor, such as a sibling.

One novel approach to treatment of neuroblastomas is therapy with desferoxamine (DFO), which is ordinarily used to treat iron poisoning. DFO has been shown to have antitumor activity in neuroblastomas and other cancers of the central nervous system. It is thought that the drug works by lowering the increased iron levels in the body associated with cancer.

As of 2004, there are significant differences in treatment protocols for neuroblastoma between the major North American study group (Children's Oncology Group) and its European counterpart, the Société Internationale d'Oncologie Pédiatrique (SIOP). These differences include biopsy techniques, the timing and extent of surgery, chemotherapy dosages, and the types of salvage therapy employed.

Prognosis

The chances of recovery from neuroblastoma depend on the stage of the cancer, the age of the child at diagnosis, the location of the tumor, and the state and nature of the tumor cells evaluated under the microscope. Infants have a higher rate of cure than do children over one year of age, even when the disease has spread. In general, the prognosis for a young child with neuroblastoma is good: the predicted five-year survival rate is approximately 85% for children who had the onset of the disease in infancy, and 35% for those whose disease developed later.

Alternative and complementary therapies

No alternative therapy has yet been reported to substitute for conventional neuroblastoma treatment. Complementary therapies—such as retinoic acid therapy—have been shown to be beneficial to patients when administered after a conventional course of chemotherapy or transplantation.

Coping with cancer treatment

Neuroblastoma is a childhood cancer and it must be recognized that children, adolescents and their families have very special needs. These are best met at cancer centers for children working in close contact with the

QUESTIONS TO ASK THE DOCTOR

- What treatment choices do we have?
- Has the neuroblastoma spread to other parts of the body?
- What is the stage of the cancer?
- Based on your experience in treating neuroblastoma, how long do you think my child will survive if there is no response to treatment or the cancer comes back?
- How long will it take to recover from treatment?
- Will my child develop any long-term risks or complications from the cancer or its treatment?
- Can you recommend a support group in my town for people who are coping with neuroblastoma?

treatment team and the primary care physician. These centers have experience in recognizing the unique needs of children having to cope with cancer and they are staffed by pediatric support professionals other than the oncology treatment team while being associated with a children's hospital.

Clinical trials

As of 2004, the National Cancer Institute supported over 55 neuroblastoma **clinical trials** to evaluate a variety of anticancer drugs either combined to other drugs or to other treatments. No fewer than 14 of these studies involve stem cell transplantation, alone or in combination with other forms of treatment. Other clinical trials are concerned with anticancer drugs that are still considered investigational.

Prevention

Neuroblastoma may be a genetic disease passed down from the parents. In 2004, a group of German researchers reported that a series of neuroblastomas demonstrated a consistent pattern of deletions and overrepresentations on chromosomes 3, 10, 17q, and 20. There is currently no known method for its prevention.

Special concerns

After completion of a course of treatment for neuroblastoma, physicians sometimes recommend that the child undergo an investigative operation. This procedure allows the treatment team to evaluate how effective treatment has been, and may offer an opportunity to remove more of the tumor if it is still present.

See also Bone marrow aspiration and biopsy.

Resources

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ORGANIZATIONS

The American Cancer Society (1-800-ACS-2345) provides information on specific types of cancer and a variety of cancer-related subjects. Additionally, it distributes booklets which can help cope with cancer treatment. Examples are: After Diagnosis: A Guide for Patients and Families (Booklet, Code #9440); Caring for the Patient with Cancer at Home (Booklet, Code #4656);

Understanding Chemotherapy: A Guide for Patients and Families (Booklet, Code #9458); Understanding Radiation Therapy: A Guide for Patients and Families (Booklet, Code #9459).

National Cancer Institute. Office of Cancer Communications, 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. 800-422-6237. <http://cancernet.nci.nih.gov/clinpdq/pif/Neuroblastoma_Patient.html.>.

National Institutes of Health & National Cancer Institute. *Young People With Cancer: A Handbook for Parents*. <http://www.cancernet.nci.nih.gov/young_people/yngconts.html>.

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Neuroendocrine tumors

Definition

Neuroendocrine tumors are tumors that develop from the cells of the diffuse neuroendocrine system, such as the enterochromaffin (EC) cells. These tumors are characterized by the presence of cells that possess secretory granules and have the ability to secrete neurohormones.

Description

The endocrine system is a network of glands consisting of endocrine cells that produce hormones in the body. The neuroendocrine system cells are specialized endocrine cells of the nervous system and produce neurohormones. Neuroendocrine cells do not form a specific gland; instead, they are found distributed in a wide variety of body organs where they help regulate body function.

Neuroendocrine tumors therefore represent a large class of cancers that can occur wherever neuroendocrine cells are found throughout the body. They are sometimes called carcinoid tumors, but it would be more accurate to consider these tumors as a sub-category of the larger family of neuroendocrine tumors. Neuroendocrine tumors are most often found in the digestive system and the lung. Statistically, 38% occur in the appendix, 23% in the ileum, 13% in the rectum, and 11.5% in the bronchi. Neuroendocrine pancreatic tumors are rather rare cancers with an incidence of 1-2 cases per 100,000 people. They occur with the same frequency in men and women and the average age at diagnosis is 53 years. Neuroendocrine tumors are also known as apudomas, or tumors that contain apud cells. These cells release excessive amounts of a variety of neurohormones in the bloodstream with chemical composition that varies with location, as does their effect on the body. Neuroendocrine tumors therefore have symptoms that vary with location. Unlike other cancers that are located in a specific organ, the hormone-releasing action of these tumors causes other symptoms to appear in many other organs of the body as well. The majority of neuroendocrine tumors can give rise to metastases with time if they are left untreated.

The total incidence of neuroendocrine tumors is thought to be between five and nine million people in the United States. It is possible that these tumors are underreported because they grow slowly and do not always produce dramatic symptoms.

Types of cancers

Because they can occur wherever neuroendocrine cells are found, neuroendocrine tumors come in a wide variety of types and have been classified according to their site of origin, usually either as digestive system, pancreatic or lung neuroendocrine tumors.

Neuroendocrine tumors of the digestive system

The types of neuroendocrine tumors found in the digestive system are also indicative of their general location:

- Foregut neuroendocrine tumors. Foregut tumors arise in the stomach or duodenum (first part of the small intestine) and represent approximately 15% to 25% of neuroendocrine tumors.
- Midgut neuroendocrine tumors. Midgut tumors are the most common variety and they include small and large intestine tumors.
- Hindgut neuroendocrine tumors. Hindgut tumors occur less frequently and are found in parts of the colon and in the rectum.

Pancreatic neuroendocrine tumors

Most neuroendocrine pancreatic tumors produce multiple hormones but usually there is excessive production of only one hormone. This is why neuroendocrine pancreatic tumors are often classified according to the predominant hormone secreted or resulting symptoms observed. For example, insulinomas produce excessive amounts of insulin, and gastrinomas produce excessive amounts of the peptide gastrin. Glucagonomas are associated with skin lesions and irritation around the eyes,

and somatostatinomas are associated with gallstones, slight diabetes and **diarrhea** or constipation.

Lung neuroendocrine tumors

There are four main types of neuroendocrine lung tumors:

- Small-cell lung cancer (SCLC). SCLC represents one of the most rapidly growing types of cancer.
- Large-cell neuroendocrine **carcinoma**. A rare form of cancer, similar to SCLC in prognosis and treatment, except that the cancer cells are unusually large.
- Typical carcinoid tumors. These types of neuroendocrine lung tumors grow slowly and do not often spread beyond the lungs.
- Atypical carcinoid tumors. Atypical lung carcinoids tumors grow faster than the typical tumors and are more likely to metastasize to other organs.

Other classifications for neuroendocrine tumors

Additionally, neuroendocrine tumors are subclassified into "functionally active" and "functionally inactive" tumors. Functionally active neuroendocrine tumors display specific symptoms, such as the excessive release of specific neurohormones from the tumor cell, as described above for pancreatic neuroendocrine tumors.

A recent classification groups neuroendocrine tumors into two types, depending on the kind of cells they develop from:

- Group I (epithelial). This group includes neuroendocrine carcinomas, graded 1, 2, and 3. Grade 1 neuroendocrine carcinomas are also known as carcinoid tumors. Grade 2 include tumors such as atypical carcinoid tumors, medullary thyroid carcinomas, and some pancreatic endocrine tumors. Grade 3 includes small-cell as well as large-cell neuroendocrine carcinomas.
- Group II (neural). Group II neuroendocrine tumors include paragangliomas, neuroblastomas, primitive neuroectodermal tumors, medulloblastomas, retinoblastomas, pineoblastomas and peripheral neuroepitheliomas.

Diagnosis

The diagnosis of carcinoid syndrome is made by the measurement of 5–hydroxy indole acetic acid (5–HIAA) in the urine. 5–HIAA is a breakdown (waste) product of serotonin. If the syndrome is diagnosed, the presence of carcinoid tumor is a given. When the syndrome is not present, diagnosis may be delayed, due to the vague symptoms present. Diagnosis can sometimes take up to two years. It is made by performing a number of tests, and the specific test used depends on the tumor's suspected location. The tests that may be performed include gastrointestinal endoscopy, **chest x ray**, computed tomography scan (CT scan), **magnetic resonance imaging**, or ultrasound. A biopsy of the tumor is performed for diagnosis. A variety of hormones can be measured in the blood as well to indicate the presence of a carcinoid.

Treatment

The only effective treatment for carcinoid tumor is surgical removal of the tumor. Although **chemotherapy** is sometimes used when metastasis has occurred, it is rarely effective. The treatment for carcinoid syndrome is typically meant to decrease the severity of symptoms. Patients should avoid **stress** as well as foods that bring on the syndrome. Some medications can be given for symptomatic relief; for example, tumors of the gastrointestinal tract may be treated with octreotide (Sandostatin) or lanreotide (Somatuline) to relieve such symptoms as diarrhea and flushing. These drugs are known as somatostatin analogs.

Liver transplantation is a treatment option for patients with neuroendocrine tumors that have metastasized only to the liver. As of 2004, this approach is reported to offer patients long disease-free periods and relief of symptoms.

Prognosis

The prognosis of carcinoid tumors is related to the specific growth patterns of that tumor, as well as its location. For example, a group of researchers at the University of Wisconsin reported in 2004 that patients with gastrointestinal tumors in the hindgut had longer periods of disease-free survival than those with foregut or midgut cancers. For localized disease the five-year survival rate can be 94%, whereas for patients where metastasis has occurred, the average five-year survival rate is 18%. It is not unusual for patients with carcinoid tumors to live ten or fifteen years after the initial diagnosis.

Prevention

Neuroendocrine tumors such as carcinoid tumors are rare, and no information consequently is yet available on cause or prevention.

See also Adenoma; Carcinoid tumors, gastrointestinal; Carcinoid tumors, lung; Cushing's syndrome; Endocrine system tumors; Lung cancer, small cell; Merkel cell carcinoma; Pancreatic cancer, endocrine; Parathyroid cancer; Pituitary tumors; Zollinger-Ellison syndrome.

KEY TERMS

Apudoma—A tumor capable of Amine Precursor Uptake and Decarboxylation (APUD).

Bronchi—Air passages to the lungs.

Diffuse neuroendocrine system—Concept developed by Feyrter, a German pathologist, more than 60 years ago, to unify tumors that occur in various parts of the body and possess secretory activity as well as similar properties when examined under a microscope.

Epithelial cells—Cells that cover the surface of the body and line its cavities.

Gastrointestinal tract—The GI tract, also called the digestive tract, starts from the oral cavity (mouth) and proceeds to the esophagus, the stomach, the duodenum, the small intestine, the large intestine (colon), the rectum and the anus. It processes all the food we eat. Along its way, food is digested, nutrients are extracted and waste is eliminated from the body in the form of stool and urine.

Gland—An organ that produces and releases substances for use in the body, such as fluids or hormones.

Hormone—Chemical substances produced by endocrine glands and transported by the bloodstream to the organs which require them to regulate their function.

Ileum—The last portion of the small intestine.

Metastasis—The transfer of cancer from one location or organ to another one not directly related to it.

Nervous system—The network of nerve tissue of the body. It includes the brain, the spinal cord and the ganglia (group of nerve cells).

Neurohormone—A hormone produced by specialized neurons or neuroendocrine cells.

Neuron—Specialized cell of the nervous system, that transmits nervous system signals. It consists of a cell body linked to a long branch (axon) and to several short ones (dendrites).

Syndrome—A series of symptoms or medical events occurring together and pointing to a single disease as the cause.

Resources

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The Carcinoid Cancer Foundation, Inc. 1751 York Avenue, New York, NY 10128. Phone:(888)722-3132 or (212)722–3132. Web site: <http://www.carcinoid.org/>.

OTHER

The Carcinoid Cancer Online Support Group. To subscribe: <http://www.LISTSERV@LISTSERV.ACOR.ORG>.

European Neuroendocrine Tumor Network. Web site: <http://www.tentelemed.com/eunet/home.html>.

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Neurofibromatosis *see* **Von Recklinghausen's neurofibromatosis**

Neuropathy

Description

Neuropathy, also known as peripheral neuropathy, is an inflammation, injury, or degeneration of any nerve outside of the central nervous system. These nerves, known as the peripheral nerves, help the muscles to contract (motor nerves) and allow a range of sensations to be felt (sensory nerves). Peripheral nerves also help control some of the involuntary functions of the autonomic nerves, which regulate the sweat glands, blood pressure, and internal organs. Unfortunately, peripheral nerves are fragile and easily damaged. The symptoms of neuropathy depend upon the cause and on which nerve, or nerves, are involved.

In cancer patients, neuropathy may be a consequence of certain **chemotherapy** drugs, the cancers themselves, or other diseases and medications. If the sensory nerves are involved, the symptoms may include pain, numbness and tingling, burning, or a loss of feeling. If the motor nerves are affected, there may be weakness or paralysis of the muscles that control those nerves. These symptoms may begin gradually. Depending upon the specific nerves involved, symptoms can range from mild tingling or numbness in the fingers or toes to severe pain in the hands or feet. Patients may also describe these symptoms as burning, prickling, or pinching. Some patients report that the skin is so sensitive that the slightest touch is agonizing. They may also experience heaviness or weakness in the arms and legs. As neuropathy increases in severity, patients might have an unsteady gait and can have difficulty feeling the floor beneath them. Those with autonomic neuropathy might experience dizziness, constipation, difficulty urinating, impotence, vision changes, and hearing loss.

Causes

Neuropathy occurs in cancer patients for a number of reasons. The cancer itself may be infiltrating the nerves. Patients may have other diseases such as diabetes, nutritional imbalances, alcoholism, and kidney failure, which may also cause neuropathy. It is important for the physician to distinguish which factor is responsible, so the appropriate treatment can be initiated. The most common cause in cancer patients, however, is chemotherapy drugs. Neuropathy occurs in approximately 10–20% of cancer patients receiving chemotherapy. The most common chemotherapy drugs that cause neuropathy include:

- platinum compounds (e.g., **cisplatin**, carboplatin)
- taxanes (e.g., **docetaxel** and paclitaxel)
- vincristine

The following chemotherapy agents can also cause neuropathy, but the incidence is relatively small compared to the prior ones listed. These include:

- procarbazine
- cytosine Arabinoside (Ara C or cytarabine)
- metronidazole

Treatments

Not long ago, few options were available to prevent or stop the progress of peripheral neuropathy. Treatments are now available that can halt the development of chemotherapy-caused neuropathy or at least diminish its effects.

The only effective preventive therapy is the use of **amifostine** (Ethyol). Some of the side effects of this medication include temporary low blood pressure, and **nausea and vomiting**. Patients should have adequate fluid intake before and during the 15-minute intravenous administration of amifostine. Blood pressure readings should be taken every five minutes during the infusion. Chemotherapy is administered shortly after giving the amifostine so that the maximum amount of the drug is in the cells before the chemotherapy is started.

If neuropathy does develop, it may be necessary to discontinue the suspected chemotherapy drug causing it. Administration of amifostine may reverse the neuropathy or lessen its symptoms.

A variety of medications are available that can ease symptoms for those suffering from neuropathy. These medications include:

- Pain relievers. Pain medicines available over-the-counter, such as acetaminophen (Tylenol), and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen (Advil, Motrin IB, Nuprin), can help to alleviate mild symptoms. For more severe symptoms, the physician may recommend a prescription NSAID.
- Tricyclic antidepressants. Certain antidepressant medications, including **amitriptyline** (Elavil), nortriptyline (Pamelor), desipramine (Norpramin) and imipramine (Tofranil), can help with mild to moderate symptoms.
- Antiseizure medications. Certain drugs intended to treat epilepsy, such as **carbamazepine** (Tegretol) and **phenytoin** (Dilantin), can be effective in treating jabbing, shooting pain.
- Other drugs. Mexiletine (Mexitil), a drug normally used to treat irregular heart rhythms, may help to relieve burning pain.

KEY TERMS

Autonomic nervous system—The part of the nervous system that controls involuntary bodily functions.

Peripheral nervous system—The portion of the nervous system outside of the central nervous system.

The physician or pharmacist should be consulted regarding potential side effects or interactions with other medications.

Alternative and complementary therapies

Several other drug-free techniques can be helpful in providing pain relief. These are frequently used in conjunction with medication. These include:

- Biofeedback. This therapy uses a special machine to teach the patient how to control certain responses that can reduce pain.
- Transcutaneous electronic nerve stimulation (TENS). The physician may prescribe this treatment that may prevent pain signals from reaching the brain. It is generally more effective for acute pain than chronic pain.
- Acupuncture. This may be effective for chronic pain, including the pain of neuropathy.
- Hypnosis. The patient under hypnosis typically receives suggestions intended to decrease the perception of pain.
- Relaxation techniques. These techniques can help decrease the muscle tension that aggravates pain. They may include deep-breathing exercises, visualization, and meditation.

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Neutropenia

Description

Neutropenia is an abnormally low level of neutrophils in the blood. Neutrophils are white blood cells (WBCs) produced in the bone marrow and comprise approximately 60% of the blood. These cells are critically important to an **immune response** and migrate from the blood to tissues during an infection. They ingest and destroy particles and germs. Germs are microorganisms such as bacteria, protozoa, viruses, and fungus that cause disease. Neutropenia is an especially serious disorder for cancer patients who may have reduced immune functions because it makes the body vulnerable to bacterial and fungal infections. White blood cells are especially sensitive to **chemotherapy**. The number of cells killed during **radiation therapy** depends upon the dose and frequency of radiation, and how much of the body is irradiated.

Neutrophils can be segmented (segs, polys, or PMNs) or banded (bands) which are newly developed, immature neutrophils. If there is an increase in new neutrophils (bands) this may indicate that an infection is present and the body is attempting a defense. Neutropenia is sometimes called agranulocytosis or granulocytopenia because neutrophils display characteristic multi-lobed structures and granules in stained blood smears.

The normal level of neutrophils in human blood varies slightly by age and race. Infants have lower counts than older children and adults. African Americans have lower counts than Caucasians or Asians. The average adult level is 1,500 cells/mm^3 of blood. Neutrophil counts (in cells/mm^3) are interpreted as follows:

- Greater than 1,000. Normal protection against infection.
- 500-1,000. Some increased risk of infection.
- 200-500. Great risk of severe infection.
- Lower than 200. Risk of overwhelming infection; requires hospital treatment with **antibiotics**.

Neutropenia has no specific symptoms except the severity of the patient's current infection. In severe neutropenia, the patient is likely to develop periodontal disease, oral and rectal ulcers, **fever**, and bacterial **pneumonia**. Fever recurring every 19–30 days suggests cyclical neutropenia.

Diagnosis is made on the basis of a white blood cell count and differential. The cause of neutropenia can be difficult to establish and depends on a combination of the patient's history, genetic evaluation, bone marrow **biopsy**, and repeated measurements of the WBC. However, in cancer patients it is usually an expected side effect of chemotherapy or radiation. The overall risk of infection is dependent upon the type of cancer an individual has as well as the treatment received. Patients at greater risk include those with hematologic malignancies, leukemia/lymphoma (cancers) and those who receive bone marrow transplants.

It is important to detect infections early. Some signs that indicate infection include:

- coughing and difficulty breathing, congestion
- an oral temperature greater than 105° with typical fever symptoms of chills and sweating
- problems in the mouth such as white patches, sore and swollen gums
- changes in urination or in stools
- drainage and pain from any cuts or tubes used in the cancer treatments such as catheters and feeding tubes
- an overall feeling of illness

Causes

Neutropenia may result from three processes:

Decreased WBC production

Lowered production of white blood cells is the most common cause of neutropenia. It can result from:

- Cancer, including certain types of leukemia.
- Radiation therapy.
- Medications that affect the bone marrow, including cancer drugs (chemotherapy), chloramphenicol (Chloromycetin), anticonvulsant medications, and antipsychotic drugs (Thorazine, Prolixin, and other phenothiazines). In hematopoietic stem cell transplantation (HSCT), high levels of total body irradiation (TBI) or chemotherapy are used to kill cancer cells, or these treatments may be combined. Two types of HSCT treatments are **bone marrow transplantation** (BMT) and peripheral blood stem cell transplantation (PBSCT). During the treatment process, the patient's normal bone marrow stem cells are killed along with the cancer cells. The stem cells are not able to mature into immune cells such as neutrophils, causing neutropenia. To reduce neutropenia, the normal stem cells

KEY TERMS

Cyclical neutropenia—A rare genetic blood disorder in which the patient's neutrophil level drops below 500/mm^3 for six to eight days every three weeks.

Cytokine—A type of protein produced by immune cells that affects the actions of other cells.

Differential—A blood cell count in which the percentages of cell types are calculated as well as the total number of cells.

Filigrastim—G-CSF cytokine normally produced in the body at low levels. G-CSF helps the body produce more neutrophils to fight infection.

Granulocyte—Any of several types of white blood cells that have granules in their cell substance. Neutrophils are the most common type of granulocyte.

Neutrophil—A granular white blood cell that ingests bacteria, dead tissue cells, and foreign matter.

Opportunistic infection— A type of infection caused by an organism that would not normally cause disease in a healthy person, but can do so when the immune system of the host is weakened.

Sargramostim—A medication made from yeast that stimulates WBC production. It is sold under the trade names Leukine and Prokine.

Sequestration and margination—The removal of neutrophils from circulating blood by cell changes that trap them in the lungs and spleen.

from the patient may be removed prior to treatment and given back at a later time. Cells can also be supplied from another donor.

- Hereditary and congenital disorders that affect the bone marrow, including familial neutropenia, cyclic neutropenia, and infantile agranulocytosis.
- Exposure to pesticides.
- Vitamin B_{12} and folate (**folic acid**) deficiency.

Destruction of White Blood Cells

WBCs are used and die at a faster rate by:

- Acute bacterial infections in adults.
- Infections in newborns.
- Certain autoimmune disorders, including systemic lupus erythematosus (SLE).
- Penicillin, **phenytoin** (Dilantin), and sulfonamide medications (Benemid, Bactrim, Gantanol).

Sequestration and margination of WBCs

Sequestration and margination are processes in which neutrophils are removed from the general blood circulation and redistributed within the body. These processes can occur because of:

- Hemodialysis
- Felty's syndrome, or malaria. The neutrophils accumulate in the spleen.
- Bacterial infections. The neutrophils remain in the infected tissues without returning to the bloodstream.

Special concerns

Often the infections that develop in a cancer patient are opportunistic infections. That is, the organisms responsible for the infection normally would not cause disease in a healthy person, but do so in a cancer patient because the immune system is weak. Several steps can be taken on a daily basis to reduce the risk of developing an infection.

Steps to Prevent Infection

- Care should be taken to keep the body clean. Hands should be washed after using the bathroom and before eating.
- Avoid stagnant or still water in the environment that might contain bacteria such as flower vases and birdbaths, or containers that may hold items such as dentures.
- Use antiseptic mouthwashes to cleanse the mouth. Use those that do not contain alcohol.
- Use deodorant. Antiperspirants will not allow the body to sweat, trapping bacteria within the body that may increase the risk of infection.
- Women with neutropenia should consider using sanitary napkins instead of tampons during their menstruation to help prevent possible infection such as toxic shock syndrome.
- Avoid others who are ill and large crowded areas where one might encounter illness.
- Avoid activities that may increase the chance of physical injury. Take care to protect the body by wearing gloves, shoes, and other items. Tend to all injuries as soon as possible.
- Neutropenic patients should consult their doctors before receiving any vaccinations.

QUESTIONS TO ASK THE DOCTOR

- What symptoms lead to this diagnosis?
- What can be expected with this condition and how long it last?
- What is the plan for treatment? Will it be covered by my insurance? Can it be done at home?
- What support and monitoring for home health care might be available? Would supervision be required? Would this be appropriate and what are the risks of complications? What are the costs?
- What are the side effects of treatment? Are there any drugs, foods, etc. that should not be taken during treatment? Should daily activities be modified?
- What complementary and alternative treatment methods have been shown to be helpful in addition to conventional medical treatments? Have any of these treatments been helpful to reduce symptoms and side effects from medication?
- Are complementary treatments easy to access and what is the cost of such treatments? Are these covered by my insurance as well?
- Where can a person get more information about this condition?
- What avenues for emotional and spiritual support might be available to help cope with this diagnosis?

Treatments

Treatment of neutropenia depends on the underlying cause.

Medications

Patients with fever and other signs of infection are treated with antibiotics. Some antibiotics used in the treatment of cancer patients include imipenem, meropenem, aminoglycoside, antipesudomonal penicillin, rifampin, and vancomycin. Combination therapy can be used that uses several types of antibiotics to stop the infection, but some of the drugs may be toxic or costly.

Patients receiving chemotherapy for cancer may be given drugs even in health to help restore the WBC to normal. A blood growth factor called **sargramostim** (Leukine, Prokine) stimulates WBC production. Another commonly used medication to reduce neutropenia in cancer patients is the cytokine G-CSF (granulocyte colony-stimulating factor, or filgrastim by Amgen-Roche). This substance is normally produced in the body at low levels. G-CSF helps the body produce more neutrophils to fight infection. This is especially useful in that many bacteria can not be killed by antibiotics due to antibiotic resistance.

Throughout the course of treatment it is important that the patient be monitored closely. This requires hospitalization for some patients, while others may be adequately treated at home.

Alternative and complementary therapies

A healthy lifestyle should be adopted that includes good nutrition, plenty of sleep, and appropriate levels of exercise. Avoid uncooked foods that may contain harmful bacteria. A nutritionist should be consulted to determine an appropriate, healthy diet.

Psychological stress can also weaken the immune system, making a person more susceptible to illness. It is important to find emotional support through family, friends, support groups, or through spiritual means.

See also Immunologic therapies; Infection and sepsis; Chronic myelocytic leukemia.

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Night sweats

Description

Night sweats can be a side effect of cancer treatment or a symptom of certain cancers. Night sweats are part of a variety of symptoms referred to as vasomotor. Vasomotor symptoms stem from the body's thermoregulatory center, which is affected by circulating hormones.

Women may undergo **oophorectomy** (the surgical removal of one or both ovaries), either for **ovarian cancer** or when accompanied by hysterectomy for **endometrial cancer** or uterine sarcoma, as part of their cancer treatment. Pelvic radiation may also damage the ovaries. Removal or permanent damage to the ovaries results in immediate menopause. Many women with ovarian cancer have already gone through menopause, as a function of their age. However, when ovarian or reproductive tract cancer strikes a pre-menopausal woman, the immediate, versus gradual, loss of circulating hormones is dramatic, and is a concern in the immediate post-operative period. In an *American Cancer Society News Today* of January 29, 2001, the ACS reported on a study that found women undergoing systemic treatment for **breast cancer**, especially those on **tamoxifen**, reported

a higher frequency and intensity of menopausal symptoms such as night sweats, hot flashes, and **fatigue**. Men may also experience vasomotor symptoms with metastatic adenocarcinoma of the prostate, or following removal of the prostate for **prostate cancer**.

Vasomotor symptoms such as night sweats add to the existing stress for individuals undergoing cancer treatment, as they can reduce the quality of sleep, make daily life very uncomfortable, and decrease the quality of life.

Night sweats can be a sign of infection in the immuno-compromised cancer patient, as well as being a symptom of undiagnosed cancer and early AIDS. Drenching night sweats may be a sign of Hodgkin's or non-Hodgkin's **lymphoma**, both in children as well as in adults. Night sweats may also be present with liver hemangioma tumors. Generalized symptoms such as night sweats, **fever**, chills, and sweating are sometimes referred to as B symptoms. Night sweats have also been associated with malignant **melanoma** and with metastatic compression of the optic nerve. Children who are ultimately diagnosed with a malignancy may present to a rheumatologist with a variety of symptoms, including night sweats. Night sweats in the absence of explained fever or perimenopause should be brought to the attention of one's health care provider for evaluation.

Causes

The ovary produces the hormone estrogen. When the ovary is removed, there is a dramatic termination of circulating estrogen, with symptoms such as night sweats, hot flashes, and vaginal dryness. Estrogen replacement therapy (ERT) can relieve these symptoms. However, the use of ERT is controversial with some cancers, because of the association with estrogen-receptor positive cancers. Women who are approaching menopause at the time of **chemotherapy** may lose ovarian function as a result of treatment, thus undergoing significant menopausal symptoms. The use of tamoxifen in postmenopausal women has been associated with an increase in vasomotor symptoms.

Hodgkin's and non-Hodgkin's lymphomas are cancers of the lymphatic system. Symptoms include night sweats, painless swelling in the lymph nodes, especially in the neck, underarm or groin, unexplained **weight loss**, recurrent fevers, and itchy skin. The night sweats in Hodgkin's disease appears to be related to an instability in the thermoregulatory center of the hypothalamus. Risk factors for Hodgkin's and non-Hodgkin's lymphomas include reduced immune function, transplant surgery, occupational exposure to herbicides and other toxic chemicals, Sjögren's syndrome, and **Epstein-Barr virus**.

KEY TERMS

Hirsutism—The development of male-pattern hair growth as a result of the use of male hormones.

Lymphatic system—The lymphatic system is a complex network of vessels, ducts, nodes, and organs that produce, filter, and carry lymph throughout the body. It is part of the body's immune system.

Oophorectomy—Surgical removal of the ovaries.

Perimenopause—The time period prior to menopause that may last 10 to 15 years, even beginning in one's 30s. It is associated with decreased ovarian function and decreasing estrogen levels.

Vasomotor symptoms—Vasomotor symptoms include night sweats, hot flashes, and sweating.

Treatments

Some research has been conducted using estrogen-androgen replacement therapy. The concerns about ERT and estrogen-sensitive cancers remains the same. The androgen component assists in the healing process, as well as in a sense of well-being, sexual desire and arousal, and increased energy level. The use of androgens can result in hirsutism (growth of male-pattern hair), which may be dose-dependent.

Successful diagnosis of the cause of the night sweats can lead to proper treatment for the condition. Successful treatment of Hodgkin's or non-Hodgkin's lymphoma resolves the night sweats.

Alternative and complementary therapies

Acupuncture has been effective for both men and women. Individuals considering herbal remedies or supplements for reproductive-related night sweats associated with cancer treatment should seek the counsel of a knowledgeable practitioner. Substances that function through mimicking estrogenic properties could have an adverse effect in estrogen-sensitive tumors.

Resources

ORGANIZATIONS

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National Cancer Institute. Building 31, Room 10A31, 31 Center Drive, MSC 2580, Bethesda, MD 20892–2580. 301–435–3848. <http://www.nci.nih.gov>.

National Center for Complementary and Alternative Medicine. NCCAM Clearinghouse, P.O. Box 8218, Silver Spring, MD 20907-8218. (888) 644-6226. <http://nccam.nih.gov>.

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Nilutamide *see* **Antiandrogen**

Nitrogen mustard *see* **Mechlorethamine**

Non-Hodgkin's lymphoma

Definition

One of two general types of lymphomas (cancers that begin in lymphatic tissues and can invade other organs) differing from **Hodgkin's disease** (HD) by a lack of Hodgkin's-specific Reed-Sternberg cells.

Description

Non-Hodgkin's lymphoma (NHL) is a cancer of lymphocytes, a type of white blood cell that moves around the body as part of its role in the immune system. NHL is much less predictable than HD and is more likely to spread to areas beyond the lymph nodes.

NHL is comprised of approximately 10 subtypes and 20 different disease entities. Division is based on whether the lymphoma is low grade (progressing slowly) or high grade (progressing rapidly). NHL is also grouped according to cell type—B cells or T cells. Physicians can diagnose the type of lymphoma by performing a **biopsy**, in which a lymph node is removed and examined in the laboratory. Some of the Non-Hodgkin's lymphoma types include: **Burkitt's lymphoma**, diffuse large B-cell lymphoma, follicular center lymphoma, and **mantle cell lymphoma**.

Nonsteroidal anti-inflammatory drugs

Definition

Nonsteroidal antiinflammatory drugs (NSAIDs) are a type of drug that reduce pain and inflammation.

Purpose

NSAIDs often are used to relieve mild to moderate pain for all types of cancer, as well as the pain of arthritis, menstrual cramps, sore muscles following exercise, and tension headaches. Most NSAIDs are available in over-the-counter formulations.

Ibuprofen and naproxen are two NSAIDs that are also used to bring down fever and treat the side effects of radiation therapy.

Description

This class of drugs eases discomfort by blocking the pathway of an enzyme that forms prostaglandins (hormones that cause pain and swelling). By doing so, the drugs lessen the pain in different parts of the body.

Some of the NSAIDs used in cancer treatment include: ibuprofen (Motrin, Advil, Rufen, Nuprin), naproxen (Naprosyn, Naprelan, Anaprox, Aleve), nabumetone (Relafen), ketorolac, sulindac and diclofenac (Cataflam, Voltaren). The class of drugs known as Cyclooxygenase-2 inhibitors that emerged in the late 1990s for dealing with arthritis pain, such as the brand names Celebrex and Vioxx, is also considered part of the group of NSAIDS.

If NSAIDs are not strong enough to keep a cancer patient comfortable, physicians often will combine them with such opioids (narcotics) as codeine. In later stages, doctors also may combine NSAIDs with stronger opioids like morphine, to treat very severe pain.

NSAIDs also may be used to prevent **colon cancer** and other types of cancer, although scientists are still studying this experimental approach (see entry on **chemoprevention**).

Recommended dosage

Patients typically take NSAIDs on an as-needed basis. Doses vary depending on the type of NSAID being used. For example, the most common type, ibuprofen, is available over the counter in 200mg caplets, which can be taken at regular intervals throughout the day. The maximum daily dose for ibuprofen is 1,200 mgs.

Precautions

Most doctors recommend taking NSAIDs with a full glass of water. Avoid taking these drugs on an empty stomach. Smoking **cigarettes** and drinking alcohol while taking NSAIDs may irritate the stomach.

People who take NSAIDs should notify their doctors before having surgery or dental work, since these drugs can prevent wounds from healing properly.

Women who are pregnant or breastfeeding should check with their doctor before taking NSAIDs, because they may be harmful to a developing fetus or a newborn.

Diabetics, people who take aspirin, blood thinners, blood pressure medications, or steroids also should check with their doctors before taking NSAIDs.

Side effects

Many NSAID users experience mild side effects, such as an upset stomach. In 4 to 7% of cases, more serious complications develop, such as stomach ulcers. Typically, elderly people experience the most serious complications.

Common side effects include stomach upset, constipation, dizziness and headaches.

More severe side effects include stomach ulcers and bleeding ulcers. If a person has black, tarry stools or starts vomiting blood, it may be caused by a bleeding ulcer.

Kidney dysfunction is another severe complication of long-term NSAID use. Signs of kidney problems include dark yellow, brown or bloody urine. NSAID use also may cause liver function problems over longer periods of time.

To guard against ulcers, physicians may ask patients to take NSAIDs with such anti-ulcer medications as omeprazole or misoprostol. Another option is to take the NSAID in a different, non-oral form. Often topical creams or suppositories are available. Finally, doctors may decide to switch to a different type of pain killer, such as a cyclooxygenase-2 (COX-2) inhibitor like Celebrex, which may be easier on the stomach. Some studies indicate that the use of COX-2 inhibitors may postpone the need to prescribe narcotic medications for severe pain.

Some patients who have had problems with side effects from NSAIDs may benefit from acupuncture as an adjunctive treatment in pain management. A recent study done in New York found that older patients with lower back pain related to cancer reported that their pain was relieved by acupuncture with fewer side effects than those caused by NSAIDs.

KEY TERMS

Cyclooxygenase-2 inhibitor—A type of drug, such as Celebrex, that reduces pain and inflammation. Also called a COX-2 inhibitor.

Enzyme—A type of protein that speeds up the chemical reactions in the body.

NSAIDs—A category of drugs that reduce pain, fever and swelling.

Opioids—A class of pain-killing drugs either derived directly from the opium poppy or from synthetic compounds resembling morphine. Opioids are also known as narcotics.

Prostaglandins—Hormones that cause pain and swelling in the body.

Interactions

NSAIDs can be taken with most other prescription and over-the-counter drugs without any harmful interactions. Certain drug combinations, however, should be avoided. For instance, when ibuprofen is combined with **methotrexate** (used for **chemotherapy** and arthritis treatment) or certain diabetic medicines and anti-depressants, it can amplify negative side effects. Patients should check with a pharmacist before taking NSAIDs with other drugs.

NSAIDs may also interact with certain herbal preparations sold as dietary supplements. Among the herbs known to interact with NSAIDs are bearberry (*Arctostaphylos uva-ursi*), feverfew (*Tanacetum parthenium*), evening primrose (*Oenothera biennis*), and gossypol, a pigment obtained from cottonseed oil and used as a male contraceptive. In most cases, the herb increases the tendency of NSAIDs to irritate the digestive tract. It is just as important for patients to inform their doctors of herbal remedies that they take on a regular basis as it is to give the doctors lists of their other prescription medications.

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U. S. Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857. (888) 463–6332. <http://www.fda.gov>.

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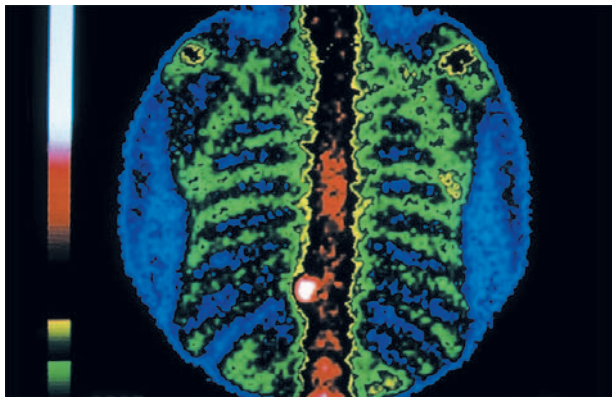
NSAIDs *see* **Nonsteroidal antiinflammatory drugs**



False-color bone scintigram (nuclear bone scan) of a person suffering from a secondary (metastatic) bone cancer (white area) affecting the dorsal spine. *(Copyright CNRI, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Nuclear medicine scans

Definition

A nuclear medicine scan is a test in which radioactive material is taken into the body and is used to create an image of a specific organ or bone.

Purpose

The purpose of a nuclear medicine scan is to locate areas of impaired function in the organ or bone being scanned. Nuclear medicine scans are widely used for diagnosis and monitoring of many different conditions. In the diagnosis and treatment of cancer, nuclear medicine scans are used to identify cancerous sites, for tumor localization and staging, and to judge response to therapy.

Precautions

Women who are pregnant or breast feeding should not undergo this test. A patient who is unable to remain still for an extended period of time may require sedation for a nuclear medicine scan.

Description

A nuclear medicine scan is an extremely sensitive test that can provide information about the structure and function of specific parts of the body. Types of nuclear scans include bone scans, heart scans, lung scans, kidney and bladder scans, thyroid scans, liver and spleen scans, and gallbladder scans. Brain scans are done to detect malignancy.

In a nuclear medicine scan, a small amount of radioactive material, or tracer, is injected or taken orally by the patient. After a period of time during which the radioactive material accumulates in one area of the body, a scan is taken by a special radiation detector, called a

KEY TERMS

Tracer—A radioactive, or radiation-emitting, substance used in a nuclear medicine scan.

radionuclide scanner. This machine produces an image of the area for analysis by the medical team.

This test is performed in a radiology facility, either in a hospital department or an outpatient x-ray center. During the scan, the patient lies on his or her back on a table, but may be repositioned to the stomach or side during the study. The radionuclide scanner is positioned against the body part to be examined. Either the camera, the table, or both, may change position during the study. Depending on the type of scan, the procedure may take anywhere from 15 to 60 minutes. It is important for the patient not to move except when directed to do so by the technologist.

Preparation

The required preparation for nuclear medicine scans ranges from slight to none. The doctor may advise that certain prescription medications be discontinued before the test or that the patient not eat for three to four hours before the test. Depending on the type of test, a reference scan or specialized blood studies may be done before the scan is taken. Jewelry or metallic objects should be removed.

The patient should advise the doctor of any previously administered nuclear medicine scans, recent surgeries, sensitivities to drugs, allergies, prescription medications, and if there is a chance that she is pregnant.

Aftercare

No special care is required after the test. Fluids are encouraged after the scan to aid in the excretion of the radioactive material. It should be almost completely eliminated from the body within 24 hours.

Risks

The risks of nuclear medicine scans are very low. Most scans use the same or less amount of radiation as a conventional **x ray** and the radioactive material is quickly passed through the body. Side effects or negative reactions to the test are very rare.

Normal results

A normal result is a scan that shows the expected distribution of the tracer and no unusual shape, size, or function of the scanned organ.

QUESTIONS TO ASK THE DOCTOR

- How long will my scan take?
- How long will the tracer stay in my body?
- Will repeat scans be necessary?

Abnormal results

Depending on the tracer and technique used, the scan can identify and image particular types of tumors or certain cancers. Too much tracer in the spleen and bones, compared to the liver, can indicate potential hypertension or cirrhosis. Liver diseases such as hepatitis may also cause an abnormal scan, but are rarely diagnosed from the information revealed by this study alone.

In a bone scan, a high concentration of tracer occurs in areas of increased bone activity. These regions appear brighter and may be referred to as "hot spots." They may indicate healing fractures, tumors, infections, or other processes that trigger new bone formation. Lower concentrations of tracer may be called "cold spots." Poor blood flow to an area of bone, or bone destruction from a tumor, may produce a cold spot.

See also Imaging studies; Magnetic resonance imaging.

Resources

ORGANIZATIONS

Society of Nuclear Medicine. 1850 Samuel Morse Dr., Reston, Virginia 20190. (703) 708-9000. Fax (703) 708–9015. <http://www.snm.org>.

OTHER

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Nutritional support

Description

Achieving adequate nutritional support is difficult during cancer therapy or treatment. However, preservation of body composition and proper nutrition will help

to maintain strength and may improve daily function and ability to cope with cancer therapies. Adequate nutrition may contribute to a patient feeling better and stronger and may help to fight off infection.

Malnutrition is a primary concern and is an important cause of illness in cancer patients due to difficulty consuming enough calories and nutrients. Protein-energy malnutrition (or protein-calorie malnutrition) is particularly problematic, which is the most common secondary illness in cancer patients. It occurs when a lack of protein and energy (calories) are consumed to sustain the body composition, instigating **weight loss**. When body stores are severely compromised, the body's functionality declines, which may lead to illness and perhaps death. Exhaustion, weakness, decreased resistance to infection, progress wasting, and difficulties tolerating cancer therapies may result from inadequate nutrition.

People with cancer commonly experience **anorexia**, which is characterized by a loss of appetite. Anorexia is the most predominate cause of malnutrition and deterioration in patients with cancer. Another common problem in cancer is weight loss and cachexia. Cachexia is a condition where the bodyweight wastes away, characterized by a constant loss of weight, muscle, and fat. It is known as a wasting syndrome and can occur in individuals who consume enough food, but due to disease complications, cannot absorb enough nutrients. Malnutrition, anorexia, and cachexia are serious in cancer patients and can lead to death.

Causes

There are many reasons for malnutrition in cancer patients, including the effect of the tumor, effect of treatment, or psychological issues such as **depression**. The growth of tumors in the digestive system may induce blockage, lead to **nausea and vomiting**, or cause poor digestion or absorption of nutrients.

Cancer therapies and their side effects may also lead to nutrition difficulties. For example, following surgery, malabsorption of protein and fat may occur. In addition, there may be an increased requirement for energy due to infection or **fever**.

Special concerns

Cancer patients should maintain an adequate intake of fluids, energy, and protein. The patient's nutrient requirements can be calculated by a dietitian or doctor because requirements vary considerably from patient to patient.

Enteral nutrition may be administered through a nose tube (or surgically placed tubes) for patients with eating difficulties due to upper gastrointestinal blockage such as difficulty swallowing, esophageal narrowing, tumor, stomach weakness, paralysis, or other conditions that preclude normal food intake. If the gastrointestinal tract is working and will not be affected by the cancer treatments, then enteral support is preferable. Parenteral nutrition (most often an infusion into a vein) can be used if the gut is not functioning properly or due to other reasons that prevent enteral feeding.

KEY TERMS

Anorexia—A condition where weight loss is due to a loss of appetite or lack of desire to eat.

Cachexia—A condition in which the bodyweight "wastes" away, characterized by a constant loss of weight, muscle, and fat.

Cancer—A term for diseases in which abnormal cells divide without control. Cancer cells can invade nearby tissues and can spread through the bloodstream and lymphatic system to other parts of the body.

Enteral nutrition—Feedings administered through a nose tube (or surgically placed tubes) for patients with eating difficulties.

Nutraceutical—Also called a functional food. These food products have other health promoting or disease preventing properties over and above their use as a food product. Specifically, a nutraceutical or functional food is a food for which a health claim has been authorized.

Parenteral nutrition—Feeding administered most often by an infusion into a vein. It can be used if the gut is not functioning properly or due to other reasons that prevent normal or enteral feeding.

Protein-energy (or protein-calorie) malnutrition—Not enough protein and energy are consumed to sustain the body composition, resulting in weight loss and possibly death.

Treatments

Nutritional problems related to side effects should be addressed to ensure adequate nutrition and prevent weight loss. The following suggestions will provide some helpful hints on dealing with side effects such as loss of appetite, nausea, vomiting, **fatigue**, and taste alteration. To deal with appetite loss and weight loss:

- Eat more when feeling the hungriest.
- Eat foods that are enjoyed the most.

- Eat several small meals and snacks instead of three large meals.
- Have ready-to-eat snacks on hand such as cheese and crackers, granola bars, muffins, nuts and seeds, canned puddings, ice cream, yogurt, and hard boiled eggs.
- Eat high-calorie foods and high-protein foods.
- Begin with small portions during a meal to enjoy the satisfaction of finishing a meal. Have additional servings if still hungry.
- Eat in a pleasant atmosphere with family and friends if desired.
- Make sure to consume at least 8–10 glasses of water per day to maintain fluid balance.
- Consider commercial liquid meal replacements such as Ensure.
- Discuss with a physician the possibility of using appetite-increasing medications such Megace or Marinol.

Nausea is a common side effect of several cancer treatments including surgery, **chemotherapy**, biological therapy, and radiation. If nausea is problematic, the following methods may provide relief:

- Avoid fatty, fried, spicy, greasy, or hot foods with a strong odor.
- Eat small meals frequently but slowly.
- If nausea is particularly worse in the morning, consume dry toast or crackers before getting up.
- Try consuming such foods as clear liquids, toast, crackers, yogurt, sherbet, pretzels, oatmeal, skinned chicken (baked or broiled), angel food cake, and fruits and vegetables that are soft or bland.
- Drink beverages cool or chilled.
- Hot foods may add to nausea, so consume foods at room temperature or cooler.
- Drink or sip liquids (a straw may help) throughout the day, but not during meals. Try sucking on ice chips.
- Discuss with a physician the possibility of using anti-nausea medications (also called **antiemetics**) such Zofran or Kytril.

Vomiting may occur for several reasons due to the cancer itself, treatment, or emotional upset. If vomiting occurs, the following guidelines may help:

- Do not drink or eat until vomiting has subsided, then consume small amounts of clear liquids.
- When able to tolerate clear liquids, try to consume a full liquid diet (including dairy products unless they are difficult to digest). Begin with small quantities and gradually return to a regular diet if nausea and vomiting have dissipated.

QUESTIONS TO ASK THE DOCTOR

- What effect will the treatment or disease have on my body nutritionally (i.e., on the ability to eat, digest food, absorb nutrients, energy requirements)?
- How long will the negative side effects last?
- Is there a risk of malnutrition or weight loss with this type of cancer or treatment?
- What nutrients are most important to obtain during treatment?
- Are there any nutritional supplements that may be required?

If fatigue is preventing receiving adequate nutrition, the following strategies may help:

- Try using frozen, canned, or ready-to-use foods.
- Eat high-calorie foods.
- Have ready-to-eat snacks on hand such as cheese and crackers, granola bars, muffins, nuts and seeds, canned puddings, ice cream, yogurt, and hard-boiled eggs.
- Consider using a service such as Meals on Wheels, a delivery or home care service.
- Invite friends or family over to assist with meal preparation.
- Consider commercial liquid meal replacements such as Ensure.

Taste changes can give foods a metallic or off flavor. Consider the following strategies to alleviate taste changes.

- If meats have a metallic taste, try other sources of protein such as dairy products, poultry, fish, seafood, peanut butter, eggs, seeds, nuts, tofu, and legumes.
- Use plastic utensils to decrease metallic flavor.
- Choose tart foods such as citrus juices, lemonade, cranberry juice, and pickles to help alleviate a metallic taste. If sore mouth and throat symptoms are also present, do not consume these foods.
- Consume a variety of foods.
- Try different seasonings, herbs, and sauces.

- Choose foods that look and smell good.
- Dilute drinks that are too strong or sweet with water.
- Rinse mouth often with baking soda and water.

Alternative and complementary therapies

There is no alternative or complementary nutritional therapy that has proven effective for **cancer prevention** or cancer treatment. However, the are several foods and nutraceuticals such as garlic, plant sterols, green and black tea polyphenols, and soybean products (soy isoflavones) that have shown promise in previous research for anticarcinogenic properties. Many of these products are actively being tested in **clinical trials** to elucidate anticarcinogenic properties. As for prevention, past research has clearly demonstrated that intake of fruits and vegetables are correlated to a lower incidence rate for certain types of cancer. It is important to check with a dietitian or doctor before taking nutritional supplements or alternative therapies because they may interfere with cancer medications or treatments.

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ORGANIZATIONS

The National Cancer Institute (NCI). Public Inquiries Office, Building 31, Room 10A31, 31 Center Drive, MSC 2580, Betheseda, MD 20892-2580. 301-435-3848, 800-4-CANCER. <http://cancer.gov/publications/>. <http://cancertrials.nci.nih.gov>. <http://cancernet.nci.nih.gov>.

National Center for Complementary and Alternative Medicine (NCCAM). 31 Center Dr., Room #5B–58, Bethesda, MD 20892-2182. 800-NIH-NCAM. Fax 301-495-4957. <http://nccam.nih.gov>.

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Nystatin *see* **Antifungal therapy**

O

Occupational exposures and cancer

Definition

Occupational exposure to cancer occurs at the workplace. Some individuals develop cancer from exposure to certain substances at an indoor workplace such as a factory or a restaurant. Others may be exposed to carcinogenic substances while working primarily outdoors, such as construction or lawn maintenance workers.

Description

About 5% of cancer in men and 1% of cancer in women result from exposure to carcinogenic substances in their work environment. The most common cancers associated with occupational exposure are:

- lung and pleura
- bladder
- skin
- laryngeal
- nasal cavity
- leukemia
- throat
- **lymphoma**
- soft-tissue sarcomas
- liver

Causes

Tobacco smoking is considered the greatest risk factor for lung cancer. Individuals who do not smoke can still develop lung cancer. Employees in smoke-filled environments such as bars, restaurants, casinos, bingo halls, and bowling alleys are at greatest risk from second-hand smoke. Second-hand smoke is highly toxic. For instance, non-smokers who live with a smoker are at 30% greater risk of developing lung cancer than if they lived with a non-smoker. However, many states, and now other countries, have worked on laws to ban smoking in some work environments.

Asbestos is a known carcinogen. Individuals whose work exposes them to asbestos are seven times more likely to die from lung cancer. Asbestos workers who smoke are 50–90 times more likely to develop lung cancer than the average individual. Asbestos affects the lining of the lungs, causing malignant **mesothelioma**. Mesothelioma is considered incurable and fatal, and may not be detected until as long as 45 years after exposure. Asbestos still exists in schools, offices, factory buildings, and homes in the form of insulation. Workers who remove asbestos from buildings need to take special precautionary measures to avoid inhalation of asbestos fibers, and wear special clothing so that they do not bring home the dust on their clothes. Asbestos can affect railroad workers, ship builders, gas mask manufacturers, and workers in insulation factories. Because of the way in which asbestos in inhaled and processed in the body, it can also lead to cancers of the larynx, esophagus, pancreas, kidney, and colon.

Radon is another substance that can cause lung cancer. Houses or commercial properties that are built on soil containing radon may contain radon in gas form. Many inhaled chemicals put workers at risk. This includes uranium and talc miners and workers who are exposed to the chemicals arsenic, vinyl chloride, nickel chromates, coal products, mustard gas, and chloromethyl ethers. While these industries need to provide safety gear to protect workers from these substances, it is always best if the worker makes sure she or he is properly protected.

Workers who are exposed to diesel fumes, such as railroad crews and truck drivers, may have a 40% greater risk of lung cancer. Diesel fumes contain benzene, formaldehyde, and dioxins. Formaldehyde alone can cause respiratory cancers. It also is used as a sterilizing agent

in dialysis units, disinfectant in operating rooms, carpet and furniture glues, as well as for embalming.

Painters, printers, and chemists are also at increased risk for lung cancer because of their occupational exposure to certain chemicals. Employees exposed to fine silica particles also have an increased risk for lung cancer. Silica appears in sand, rock, and mineral ores, and is used in sandblasting, masonry work, tunnel construction, ceramics, laying railroad track, soap manufacturing, glass manufacturing, shipbuilding, and agriculture.

Bladder cancer from occupational exposure is most common in individuals working with radiation or dyes that involve the aromatic amine chemicals such as benzidine and beta naphthylamine. Factory workers involved in the production of these dyes, as well as those who use these dyes, such as hair colorists, and possibly even people who apply their own permanent hair dye at least once a month may be at increased risk for bladder cancer.

Chemicals used in the rubber, leather, textile, and paint industries can also be carcinogenic. The risk of bladder cancer rises with age, and smoking increases significantly the risk of developing bladder cancer. Individuals who have taken the herb *Aristocholia fangchi* as part of an herbal **weight loss** product may also be at higher risk for bladder cancer. Drinking at least 11 cups of fluid a day can decrease the risk of bladder cancer, as it increases urination and decreases the concentration and the amount of time that carcinogenic substances come into contact with the bladder lining.

There are several types of skin cancer, varying in aggressiveness. Basal and squamous cell cancers are considered very curable. **Melanoma** is the most serious type, and the most likely to metastasize. Exposure to ultraviolet rays, coal tar, pitch, creosote, arsenic, and radium can lead to skin cancer. Individuals whose work is primarily outdoors, such as employees of road and building construction, landscaping, outdoor painting, and beach and boating work are at greater risk. A 2004 study in Germany found a dose-dependent relationship with exposure. In other words, the more UV rays workers were exposed to, the higher their risk proportionately rose. Using sunscreen and protective clothing such as a long-sleeved shirt, long pants, and a wide-brimmed hat can decrease exposure.

Laryngeal cancer. Individuals whose work includes heavy exposure to wood dust, paint fumes, and asbestos, and workers exposed to certain chemicals in the metal-working, petroleum, plastic, and textile industries are at increased risk for laryngeal and hypopharyngeal cancers. Tobacco and heavy alcohol use can increase the risk for these cancers by as much as 100 times.

KEY TERMS

Carcinogen—A substance, method, or process that has been scientifically shown to be a causative factor in the development of a certain cancer.

Metastasize—The ability of a cancer to spread from its site of origin to other sites in the body. The more a cancer has metastasized, the worse is the individual's prognosis for cure.

Pleura—The pleura is a membrane that covers the lungs, and lines the chest cavity.

Farmers and others who have long-term exposure to herbicides and pesticides are at increased risk for leukemia. Children whose parent has **chronic lymphocytic leukemia** (CLL) have two to four times greater risk of getting CLL themselves. Long-term exposure to benzene places the employee at greater risk of developing **acute leukemia**. Herbicides and pesticides are both associated with the development of lymphomas, so workers involved in their production as well as their application are at increased risk. Children exposed to pesticides on a regular basis are significantly more likely to develop non-Hodgkin's lymphoma than children not exposed.

Farmers appear to have an increased incidence of **prostate cancer**. The reason is not yet clear. While some have suggested it may be due to a diet high in red meat and fatty foods, studies are investigating the link between prostate cancer and pesticides, fertilizers, chemical solvents, and farm equipment fumes. Salivary gland cancer may be linked to working with nickel alloy and silica dust, and exposure to radioactive substances.

Pancreatic cancer appears to be associated with significant exposure to pesticides, certain dyes, and chemicals found in gasoline. Occupational exposure to asbestos, cadmium, and organic solvents (especially trichloroethylene) seems to increase the risk of getting kidney cancer. Dioxin is a known carcinogen, and may be a causative factor in a variety of cancers. It is a byproduct in industrial processing that deals with chlorine and hydrocarbons, such as found in incinerators and paper and pulp factories.

Other chemicals linked with cancer are DDT and PCBs (polychlorinated biphenols). Health care professionals, both human and veterinary, may be exposed to carcinogenic substances in caring for their patients. Body fluid exposure can increase the risk of hepatitis B and hepatitis C, cause liver failure, and increase the risk of liver cancer. HIV can cause AIDS and increase the risk of a variety of malignant tumors. Chemicals in paint and paint solvents are also used in ceramic factories.

QUESTIONS TO ASK THE DOCTOR

- What type and stage is my cancer?
- What do you think is the cause of my cancer?
- Will I be able to work during my cancer treatment?
- Will I be able to go back to my same job after treatment is finished?
- If not, what kind of limitations will there be on my activity level?
- What kind of work will I be able to do when my treatment is over?
- Is anyone at home at risk for cancer or illness because of my work?

Electric and magnetic fields surround electric tools and machinery. Studies have been done to investigate whether these fields are harmful to humans. Research findings continue to be controversial, some showing an increased incidence of cancers, others not finding an association. However, federally funded research studies continue.

Special concerns

Cancers that originate in the workplace do not require different treatment than if the same cancer had developed from another source. However, workers who develop cancer through occupational exposure may not be able to return to the same job, perhaps not even the same company. This means that even if the individual has survived the cancer, and gone though all that treatment entails, they cannot pick up their life where they left it at the time of the cancer diagnosis. They may be disabled, and not be able to work at all, or they may have to retrain for work, either a different job within the same company, or a whole new job and environment.

If the person is older, he or she may be less employable after illness because of age. Depending on the type of cancer, it may be difficult to prove that the work environment was a causal factor in the development of the disease. This can make it harder to obtain work-related benefits. Consequently, financial concerns may be a great burden. Also, certain cancers may have developed from the inhalation of substances that were also brought home on the employee's clothing. Others in the family may have gotten ill as well. Fine dust particles can come home on workers' clothing, shoes, skin, hair, facial hair, tools or lunch boxes, and on the inside or outside of their car.

Workers in any occupation need to be fully informed of the substances with which they come in contact. Federal regulations are in place to improve employee safety, but the regulations are ineffective if the employees do not utilize the protective clothing, masks, and other safety measures at their disposal. Individuals who learned their trade prior to the installation of many safety measures may find it difficult to *retrain* themselves with the new equipment. But not doing so may raise their risk of cancer.

While many cancers have an unknown source, cancers due to occupational exposures have known sources. This means that they are preventable, if proper safety equipment is used all of the time, and always used correctly.

Treatments

Treatments for cancers due to occupational exposure should be the same as for the same cancer developed from a different source. Treatment will depend on the type and stage of the cancer diagnosed, as well as the age and fertility needs of the patient. Access to treatment may vary, however, depending on the type of insurance the individual holds. Access to experimental treatments, or treatment that a **health insurance** deems experimental can vary.

Alternative and complementary therapies

Alternative therapy options for cancer due to occupational exposure should be the same as if the cancer developed from another source. Complementary treatments that improve the functioning of the body's immune system, or that decrease treatment side effects such as nausea, can be helpful. There may be different stresses in the life of the person with a work-related cancer. So therapies such as meditation, guided imagery, therapeutic touch, yoga, and t'ai chi can help deal with the stress of having cancer, going through treatment, and having to find alternative work options.

See also Environmental factors in cancer development.

Resources

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American Cancer Society. (800) ACS-2345. <http://www.cancer.org>.

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Octreotide *see* **Antidiarrheal agents**

Oligodendroglioma

Definition

Oligodendrogliomas are a rare form of brain tumors. The brain is made up of many supporting cells that are called glial cells. Any tumor of these glial cells is called a glioma. Oligodendrogliomas are tumors that arise from a type of glial cell called oligodendrocytes. These cells are the specialized cells of the brain that produce the fatty covering of nerve cells (myelin).

Description

Oligodendrogliomas can grow in different parts of the brain, but they are most commonly found in the frontal or temporal lobes of the cerebrum. The frontal lobes are responsible for cognitive thought processes (knowing, thinking, learning, and judging). The temporal lobes are responsible for coordination, speech, hearing, memory, and awareness of time.

There are two types of oligodendroglioma: the well-differentiated tumor, which grows relatively slowly and in a defined shape; and the anaplastic oligodendroglioma, which grows much more rapidly and does not have a well-defined shape. Anaplastic oligodendrogliomas are much less common than well-differentiated oligodendrogliomas.

More common than either form of pure oligodendroglioma is the mixed glioma, or oligoastrocytoma. These mixed gliomas are a mixture of oligodendroglioma and **astrocytoma**. An astrocytoma is a tumor that arises from the astrocytes, specialized cells in the brain that regulate the chemical environment of the brain and help to form the blood–brain barrier.

Oligodendrogliomas and mixed gliomas account for approximately 4–5% of all primary brain tumors and 10% of all gliomas. A primary brain tumor is a tumor that begins in the brain, as opposed to a secondary (or metastatic) brain tumor, which originates in another organ and spreads (metastasizes) to the brain.

Demographics

Oligodendromas occur in approximately nine in every one million people. Oligodendrogliomas can occur in people of any age, but most occur in middle-aged adults.

Oligodendrogliomas occur with equal frequency in members of all races and ethnic groups. There does not appear to be any relation of oligodendrogliomas to any geographic region. For unknown reasons, men are affected by oligodendrogliomas in higher numbers than women.

Causes and symptoms

The cause, or causes, of oligodendrogliomas are not known; however, most people with these types of tumors have some type of genetic mutation on chromosome 1, chromosome 19, or on both chromosomes 1 and 19. In early 2001, investigations were ongoing in an attempt to determine if these genetic factors, or other factors, cause oligodendrogliomas. Oligodendrogliomas are not contagious.

The symptoms of oligodenrogliomas are the result of increased pressure in the fluid within the skull (intracranial hypertension). These symptoms include:

- nausea
- vomiting
- irritability
- headache
- vision disturbances
- enlargement of the head
- seizures

Oligodendrogliomas may also be accompanied by a weakness or paralysis on the side of the body opposite to the side of the brain where the tumor is located. When the tumor is located in a frontal lobe, the patient may experience gradual changes in mood and personality. When it is located in a temporal lobe, the patient may

experience difficulty with speech, hearing, coordination, and memory.

Diagnosis

The diagnosis of oligodendrogliomas begins in the doctor's office with a basic neurological examination. This examination involves:

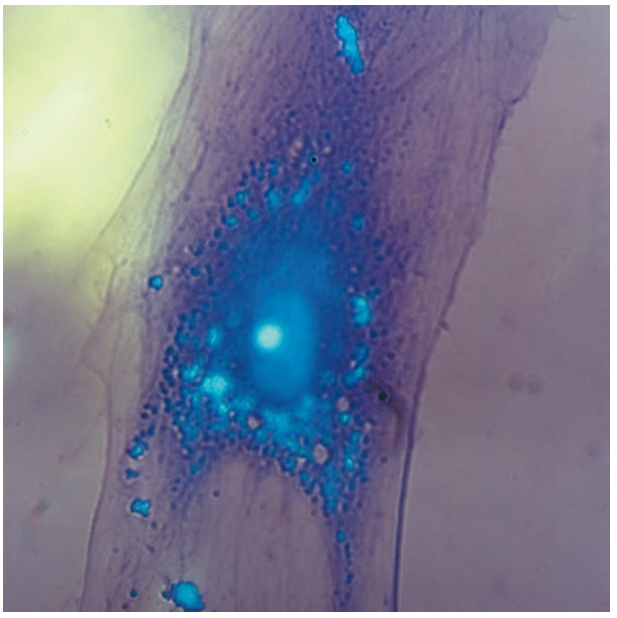
- testing eye reflexes, eye movement, and pupil reactions
- testing hearing with a tuning fork or ticking watch
- reflex tests with a rubber hammer
- balance and coordination tests
- pin-prick and cotton ball tests for sense of touch
- sense of smell tests with various odors
- facial muscle tests (e.g., smiling, frowning, etc.)
- tongue movement and gag reflex tests
- head movement tests
- mental status tests (e.g., asking what year it is, who the President is, etc.)
- abstract thinking tests (e.g., asking for the meaning of a common saying, such as "every cloud has a silver lining.")
- memory tests (e.g., asking to have a list of objects repeated, asking for details of what a patient ate for dinner last night, etc.)

If the doctor suspects a brain tumor may be present, further diagnostic tests will be ordered. These tests are performed by a neurological specialist. Imaging tests that may be ordered include computed tomography (CT) and **magnetic resonance imaging** (MRI). Other tests may include a spinal tap, to examine the cerebrospinal fluid, and an electroencephalogram (EEG), which measures the electrical activity of the brain.

Treatment team

Treatment of any primary brain tumor, including oligodendrogliomas, is different from treating tumors in other parts of the body. Brain surgery requires much more precision than most other surgeries. Also, many medicinal drugs cannot cross the blood–brain barrier. Therefore, the therapies that are used to treat oligodendrogliomas, and the side effects of these therapies, are quite complex.

The most up-to-date treatment opportunities are available from experienced, multi-disciplinary medical professional teams made up of doctors, nurses, and technologists who specialize in cancer (oncology), neurology, medical imaging, drug or **radiation therapy**, and anesthesiology.



Malignant oligodendroglioma cells from the human brain. *(Copyright Cecil Fox, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Clinical staging, treatments, and prognosis

Oligodendrogliomas and other primary brain tumors are diagnosed, or staged, in grades of severity from I to IV. Grade I tumors have cells that are not malignant and are nearly normal in appearance. Grade II tumors have cells that appear to be slightly abnormal. Grade III tumors have cells that are malignant and clearly abnormal. Grade IV, the most severe type of brain tumors, contain fast-spreading and abnormal cells. Well-defined oligodendrogliomas are generally stage I or stage II tumors. Anaplastic oligodenrogliomas are generally stage III or stage IV tumors.

The standard treatment for all grades of oligodendrogliomas is surgery to remove the tumor completely. This surgery is generally aided by an image guidance system that allows the surgeon to determine the most efficient route to location of the tumor. Approximately half of oligodendroglioma patients gain relief of the increased intracranial pressure after complete removal of their tumors. The other half require a spinal fluid shunt to allow drainage of the excess fluid.

In some instances of oligodendroglioma, the tumor is inoperable or cannot be completely removed. Patients

KEY TERMS

Anaplastic oligodendroglioma—A form of oligodendroglioma that does not have a well-defined shape and grows very rapidly and aggressively.

Astrocytoma—A type of brain tumor that arises from the astrocytes, specialized brain cells that regulate the chemical environment of the brain and form the blood-brain barrier. These types of tumors are often mixed with oligodendrogliomas to form oligoastrocytomas.

Frontal lobes—The two lobes of the cerebrum of the brain that are responsible for cognitive thought processes (knowing, thinking, learning, and judging).

Glioma—Any tumor that arises from the supporting cells in the brain called glial cells.

Intracranial hypertension—A higher-than-normal pressure of the fluid in the skull.

Oligoastrocytoma—A type of brain tumor that is a mixture of oligodendroglioma and astrocytoma. This is also called a mixed glioma.

Spinal fluid shunt—A small tube that is surgically implanted to allow excess spinal fluid to drain directly into the abdominal cavity.

Temporal lobes—The two lobes of the cerebrum of the brain that are responsible for coordination, speech, hearing, memory, and awareness of time.

Well-differentiated tumor—A tumor that grows relatively slowly and in a well-defined shape.

with inoperable oligodendrogliomas are generally treated with radiation therapies. Oligodendrogliomas are among the only brain tumors that can be successfully treated with a type of **chemotherapy** called PCV (**Procarbazine**, CCNU or **lomustine**, and **Vincristine**). Chemotherapy is usually used only in cases of recurrent anaplastic oligodendrogliomas.

For patients with well-defined oligodendrogliomas, median survival exceeds 10 years. For patients with anaplastic dendrogliomas, median survival ranges from two to five years.

Alternative and complementary therapies

For oligodendrogliomas, there are no effective alternative treatments—treatments used instead of conventional treatments like surgery or chemotherapy.

QUESTIONS TO ASK THE DOCTOR

- Which type of oligodendroglioma do I have?
- Is my tumor operable?
- What is the likelihood of my type of oligodendroglioma coming back?
- How often should I seek follow-up examinations?

Coping with cancer treatment

Most patients who undergo brain surgery to remove their tumors can resume their normal activities within a few days of the operation.

Clinical trials

There were 47 **clinical trials** underway by 2005, aimed at the treatment of oligodendrogliomas. More information on these trials, including contact information, may be found by conducting a clinical trial search at the web site of the National Cancer Institute, CancerNet <http://cancernet.nci.nih.gov/trialsrch.shtml>.

Prevention

Because the cause or causes of oligodenrogliomas are not known, there are no known preventions.

Special concerns

Repeat surgery may be necessary for oligodendrogliomas because these tumors sometimes redevelop. Careful monitoring by the medical team will be required. Also, if the tumor is located in the dominant hemisphere of the patient's brain, any treatment, especially surgery, requires special consideration and care not to disrupt the personality or other higher brain functions of the patient.

See also Brain and Central nervous system tumors.

Resources

ORGANIZATIONS

American Brain Tumor Association. 2720 River Road, Suite 146, Des Plaines, IL 60018-4110. Telephone 800-886-2282. <http://www.abta.org/>.

The Brain Tumor Society. 124 Watertown Street, Suite 3-H. Watertown, MA 02472. 617-924-9997. Fax 617-924-9998. <http://www.tbts.org/>.

National Brain Tumor Foundation. 785 Market Street, Suite 1600. San Francisco, CA 94103. Telephone 415-284-0208. <http://www.braintumor.org/>.

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Paul A. Johnson, Ed.M.

Omega-3 fatty acids

Definition

Essential to human health, omega-3 fatty acids are a form of polyunsaturated fats that are not made by the body and must be obtained from a person's food.

Purpose

Eating foods rich in omega-3 fatty acids is part of a healthy diet and helps people maintain their health.

Description

In recent years, a great deal of attention has been placed on the value of eating a low fat diet. In some cases, people have taken this advice to the extreme by adopting a diet that is far too low in fat or, worse yet, a diet that has no fat at all. But the truth is that not all fat is bad. Although it is true that trans and saturated fats, which are found in high amounts in red meat, butter, whole milk, and some prepackaged foods, have been shown to raise a person's total cholesterol, polyunsaturated fats can actually play a part in keeping cholesterol low. Two especially good fats are the omega-3 fatty acids and the omega-6 fatty acids, which are polyunsaturated.

Two types of omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), which are found mainly in oily cold-water fish, such as tuna, salmon, trout, herring, sardines, bass, swordfish, and mackerel. With the exception of seaweed, most plants do not contain EPA or DHA. However, alpha-linolenic acid (ALA), which is another kind of omega-3 fatty acid, is found in dark green leafy vegetables, flaxseed oil, fish oil, and canola oil, as well as nuts and beans, such as walnuts and soybeans. Enzymes in a person's body can convert ALA to EPA and DHA, which are the two kinds of omega-3 fatty acids easily utilized by the body.

Many experts agree that it is important to maintain a healthy balance between omega-3 fatty acids and omega-6 fatty acids. As Dr. Penny Kris-Etherton and her colleagues reported in their article published in the *American Journal of Nutrition* an over consumption of omega-6 fatty acids has resulted in an unhealthy dietary shift in the Americandiet. The authors point out that what used to be a 1:1 ratio between omega-3 and omega-6 fatty acids is now estimated to be a 10:1 ratio. This poses a problem, researchers say, because consuming some of the beneficial effects gained from omega-3 fatty acidsare negated by an over consumption of omega-6 fatty acids. For example, omega-3 fatty acids have anti-inflammatory properties, whereas omega-6 fatty acids tend to promote inflammation. Cereals, whole grain bread, margarine, and vegetable oils, such as corn, peanut, and sunflower oil, are examples of omega-6 fatty acids. In addition, people consume a lot of omega-6 fatty acid simply by eating the meat of animals that were fed grain rich in omega-6. Some experts suggest that eating one to four times more omega-6 fatty acids than omega-3 fatty acids is a reasonable ratio. In other words, as dietitians often say, the key to a healthy diet is moderation and balance.

The health benefits of omega-3 fatty acids

There is strong evidence that omega-3 fatty acids protect a person against atherosclerosis andtherefore against heart disease and stroke, as well as abnormal heart rhythms that cause sudden cardiac death, and possibly autoimmune disorders, such as lupus and rheumatoid arthritis. In fact, Drs. Dean Ornish and Mehmet Oz, renowned heart physicians, said in a 2002 article published in *O Magazine* that the benefits derived from consuming the proper daily dose of omega-3 fatty acids may help to reduce sudden cardiac death by as much as 50%. In fact, in an article published by *American Family Physician*, Dr. Maggie Covington, a clinical assistant professor at the University of Maryland, also emphasized the value of omega-3 fatty acids with regard tocardiovascular health and referred to one of the largest **clinical trials** to date, the GISSI-Prevenzione Trial, to illustrate her point. In the study, 11,324 patients with coronary heart disease were divided into four groups: one group received 300 mg of vitamin E, one group received 850 mg of omega-3 fatty acids, one group received the vitamin E and fatty acids, and one group served as the control group. After a little more than three years, "The group given omega-3 fatty acids only had a 45% reduction in sudden death and a 20% reduction in all-cause mortality," as stated by Dr. Covington.

According to the American Heart Association (AHA), the ways in which omega-3 fatty acids may reduce cardiovascular disease are still being studied. However, the AHA indicates that research as shown that omega-3 fatty acids:

- decrease the risk of arrthythmias, which can lead to sudden cardiac death
- decrease triglyceride levels
- decrease the growth rate of atherosclerotic plaque
- lower blood pressure slightly

In fact, numerous studies show that a diet rich in omega-3 fatty acids not only lowers bad cholesterol, known as LDL, but also lowers triglycerides, the fatty material that circulates in the blood. Interestingly, researchers have found that the cholesterol levels of Inuit Eskimos tend to be quite good, despite the fact that they have a high fat diet. The reason for this, research has found, is that their diet is high in fatty fish, which is loaded with omega-3 fatty acids.The same has often been said about the typical Mediterranean-style diet.

Said to reduce joint inflammation, omega-3 fatty acid supplements have been the focus of many studies attempting to validate its effectiveness in treating rheumatoid arthritis. According to a large body of research in the area, omega-3 fatty acid supplements are clearly effective in reducing the symptoms associated with rheumatoid arthritis, such as joint tenderness and stiffness. In some cases, a reduction in the amount of medication needed by rheumatoid arthritis patients has been noted.

More research needs to be done to substantiate the effectiveness of omega-3 fatty acids in treating eating disorders, attention deficit disorder, and **depression**. Some studies have indicated, for example, that children with behavioral problems and attention deficit disorder have lower than normal amounts of omega-3 fatty acids in their bodies. However, until there is more data inthese very important areas of research, a conservative approach should be taken, specially when making changes to a child's diet. Parents should to talk to their child's pediatrician to ascertain if adding more omega-3 fatty acids to their child's diet is appropriate. In addition, parents should take special care to avoid feeding their children fish high in mercury. A food list containing items rich in omega-3 fatty acids can be obtained from a licensed dietitian.

Mercury levels and concerns about safety

A great deal of media attention has been focused on the high mercury levels found in some types of fish. People concerned about fish consumption and mercury levels can review public releases on the subject issued by the U. S. Food and Drug Administration and the Environmental Protection Agency. Special precautions exist for children and pregnant or breastfeeding women. They are advised to avoid shark, mackerel, swordfish, and tilefish. However, both the U.S. Food and Drug Administration and the Environmental Protection Agency emphasis the importance of dietary fish. Fish, they caution, should not be eliminated from the diet. In fact, Robert Oh, M.D., stated in his 2005 article, which was published in *The Journal of the American Board of Family Practice* "With the potential health benefits of fish, women of childbearing age should be encouraged to eat 1 to 2 low-mercury fish meals per week."

Other concerns regarding fish safety have also been reported. In 2004, Hites and colleagues assessed organic contaminants n salmon in an article published in *Science*. Their conclusion that farmed salmon had higher concentrations of polychlorinated biphenyls than wild salmon prompted public concerns and a response from the American Cancer Society. Farmed fish in Europe was found to have higher levels of mercury than farmed salmon in North and South America; however, the American Cancer Society reminded the public that the "levels of toxins Hites and his colleagues found in the farmed salmon were still below what the U. S. Food and Drug Administration, which regulates food, considers hazardous." The American Cancer Society still continues to promote a healthy, varied diet, which includes fish as a food source.

Recommended dosage

The AHA recommends that people eat two servings of fish, such as tuna or salmon, at least twice a week. A person with coronary heart disease, according to the AHA, should consume 1 gram of omega-3 fatty acids daily through food intake, most preferably through the consumption of fatty fish. The AHA also states that "people with elevated triglycerides may need 2 to 4 grams of EPA and DHA per day provided as a supplement," which is available in liquid orcapsule form. Ground or cracked flaxseed can easily be incorporated into a person's diet by sprinkling it over salads, soup, and cereal.

Sources differ, but here are some general examples:

- 3 ounces of pickled herring = 1.2 grams of omega-3 fatty acids
- 3 ounces of salmon = 1.3 grams of omega-3 fatty acids
- 3 ounces of halibut = 1.0 grams of omega-3 fatty acids
- 3 ounces of mackerel = 1.6 grams of omega-3 fatty acids
- 1 1/2 teaspoons of flaxseeds = 3 grams of omega-3 fatty acids

Precautions

In early 2004, the U.S. Food and Drug Administration, along with the the Environmental Protection Agency, issued a statement that women who are or may be pregnant, as well as breastfeeding mothers and children, should avoid eating some types of fish thought to contain high levels of mercury. Fish that typically contain high levels of mercury are shark, swordfish, and mackerel, whereas shrimp, canned light tuna, salmon, and catfish are generally thought to have low levels of mercury. Because many people engage in fishing as a hobby, women should be sure before they eat any fish caught by friends and family that the local stream or lake is considered low in mercury.

Conflicting information exists whether it is safe for patients with macular degeneration to take omega-3 fatty acids in supplement form. Until more data becomes available, it is better for people with macular degeneration to receive their omega-3 fatty acids from the food they eat.

Side effects

Fish oil supplements can cause **diarrhea** and gas. Also, the fish oil capsules tend to have a fishy aftertaste.

Interactions

Although there are no significant drug interactions associated with eating foods containing omega-3 fatty acids, patients who are being treated with blood-thinning medications shouldn't take omega-3 fatty acid supplements without seeking the advice of their physicians. Excessive bleeding could result. For the same reason, some patients who plan to take more than 3 grams of omega-3 fatty acids in supplement form should first seek the approval of their physicians.

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Lee Ann Paradise

Ommaya reservoir

Definition

The Ommaya reservoir is a plastic, dome–shaped device, with a catheter (thin tubing) attached to the

underside used to deliver **chemotherapy** (anticancer drugs) to the central nervous system (CNS or brain and spinal cord).

Purpose

Chemotherapy may be administered to patients by various methods, depending on the type of cancer being treated. Some cancer types respond well to chemotherapy given by intravenous (IV) injection, and some cancer types may be treated with oral medication. In both cases, the chemotherapy reaches its target site systemically (carried by the blood). Cancers that affect the CNS pose a special challenge. Systemically delivered drugs seldom reach the CNS because of a network of blood vessels that surround the brain. This protective shield is called the blood–brain barrier. It acts as a filtering device for the brain by blocking the passage of foreign substances from the blood to the CNS. To avoid the obstacle created by the blood–brain barrier, alternative delivery treatments must be used. These treatments are collectively called intrathecal chemotherapy treatments. These treatments require injecting the chemotherapy directly into the cerebrospinal fluid (CSF). The CSF is the clear fluid surrounding the CNS. An oncologist (a physician specializing in cancer study and treatment) will determine the frequency of the treatment schedule and will decide if it is better for the patient to receive intrathecal chemotherapy injections directly into the spinal column or through an Ommaya reservoir implanted in the brain. The Ommaya reservoir may be used in several ways. Its primary function is to facilitate the uniform delivery of the intrathecal chemotherapy. By implanting the Ommaya reservoir, multiple rounds of chemotherapy may be given through a single access site, thereby increasing patient comfort and reducing the stress and pain associated with repeated spinal injections. The Ommaya reservoir also serves as a sampling site for removal of CSF. Samples are withdrawn an analyzed for the presence of abnormal cells. Some physicians utilize the reservoir to deliver pain medication, and more recently, trials have been conducted to test the efficacy of using the Ommaya reservoir to deliver gene therapy (treating a disease caused by a malfuncting gene, by introducing a normal gene back into the diseased individual) to cancer patients.

Precautions

High-dose chemotherapy drugs such as **methotrexate** may produce toxic effects if the reservoir or catheter becomes compromised. For infants and children being considered as candidates for an Ommaya reservoir implant, the age of the patient should be considered. Some studies have suggested that infants may be at a higher risk for post–treatment neurologic and endocrinologic problems, cognitive (learning) disabilities, and higher infant mortality when high–dose chemotherapy agents are administered via the Ommaya reservoir. These conditions are significantly reduced in adult patients. Any patient compromised by a pre–existing suppressed immune system should make the physician aware of this condition so the choice of chemotherapy and specific protocols for administering the drugs are employed.

KEY TERMS

Blood–brain barrier—The blood vessel network surrounding the brain that blocks the passage of foreign substances into the brain.

Central nervous system (CNS)—The body system composed of the brain and spinal cord.

Cerebrospinal fluid (CSF)—The fluid surrounding the brain and spinal cord.

Chemotherapy—Anticancer drugs

Intrathecal chemotherapy—Chemotherapy that must be given directly into the CSF.

Description

Placement of the Ommaya reservoir requires a minor surgical procedure with the patient placed under general anesthesia. The procedure is performed in the hospital by a neurosurgeon (a physician specially trained to perform surgery on the brain or spinal cord). The reservoir is placed under the scalp with the catheter positioned into the cavity of the brain where the CSF is formed. Once in place, chemotherapy treatments using the Ommaya reservoir may be conducted as outpatient visits either in the hospital, the home, or a satellite clinic staffed by specially trained healthcare professionals. To perform an Ommaya reservoir tap (CSF sampling and chemotherapy delivery) requires 15–20 minutes with little or no pain to the patient. Basic guidelines for the tap include:

- Remove hair from over the reservoir area.
- Gently pump the reservoir to allow the reservoir to fill with CSF.
- Clean the area with alcohol and iodine solution, maintaining a sterile field.
- The healthcare professional will insert a small needle into the reservoir and slowly withdraw a sample of CSF.

- The chemotherapy will be delivered by slowly injecting the prescribed medication into the reservoir.
- The needle is removed and the site covered with sterile gauze.
- Light pressure is applied, and the reservoir is gently pumped to enhance uniform distribution of the chemotherapy into the CSF.
- The site is covered with a Band–Aid.

Preparation

Placement of the Ommaya reservoir will require a minimal stay in the hospital. The surgeon will provide detailed pre–operative instructions for the patient prior to the hospital visit. Post–operative recovery will monitor vital signs and watch for possible side effects from the anesthesia. Before the patient is discharged, an initial round of chemotherapy administered via the Ommaya reservoir will be performed to assure the device is working properly. No special preparations are required for routine scheduled chemotherapy treatments.

Aftercare

Following an Ommaya tap, the patient may participate in all normal activities. Hair may be washed. There are no special requirements for care of the reservoir site; however, a physician should be notified if symptoms appear such as a spike in **fever**, headaches with or without vomiting, neck stiffness, tenderness, redness, or drainage at the access site of the reservoir.

Risks

The most common risks associated with the use of the Ommaya reservoir primarily deal with complications due to malposition or malfunction of the device. Either condition may result in blockage or leakage of the catheter, leading to improper drug delivery. Lesions may develop along the catheter, infection may develop, and chemotherapy may reach toxic levels. In cancer patients scheduled for surgical intervention, who have previously received chemotherapy via an Ommaya reservoir, there is some evidence of increased perioperative morbidity (a diseased condition existing at the time of surgery).

Normal results

Patients may expect successful delivery of the intrathecal chemotherapy during each treatment session with minimal discomfort. It should be noted, however, that the chemotherapy delivered by the Ommaya reservoir works on cells that are actively growing and dividing. This means both cancer cells and certain normal cell types may be affected and may result in side effects. Depressed blood cell counts may lower resistance to infection and increase susceptibility to bruising and bleeding. There may be an overall decrease in energy levels. Hair loss (alopecia) may occur, and cells of the digestive tract may be damaged resulting in bouts of nausea, vomiting, and mouth sores. For female patients, symptoms of menopause may develop, and in males, sperm production may stop.

QUESTIONS TO ASK THE DOCTOR

- What makes me a good candidate for the Ommaya reservoir?
- What types of chemotherapy will I receive?
- How often will the treatments be scheduled, and will there be side effects after each one?
- How will I know if the Ommaya reservoir is working properly?
- Is this device and procedure covered by insurance?

Abnormal results

Severe complications associated with drug delivery could occur. Due to improper function of the reservoir, toxic levels of chemotherapy could induce behavioral abnormalities, confusion, dementia, irritability, convulsions, sensory impairment, damage to pulmonary and renal function, and patient death.

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Jane Taylor-Jones, M.S., Research Associate

Ondansetron *see* **Antiemetics**

Oophorectomy

Definition

Oophorectomy is the surgical removal of one or both ovaries. It is also called ovariectomy or ovarian ablation. If one ovary is removed, a woman may continue to menstruate and have children. If both ovaries are removed, menstruation stops and a woman loses the ability to have children.

Purpose

Oophorectomy is performed to:

- remove cancerous ovaries
- remove the source of estrogen that stimulates some cancers
- remove a large ovarian cyst
- excise an abscess
- treat endometriosis
- lower the risk of an ectopic pregnancy
- lower the risk of cancer in a woman with a family history of ovarian or breast cancer

In an oophorectomy, one, or a portion of one, ovary may be removed or both ovaries may be removed. When oophorectomy is done to treat **ovarian cancer** or other spreading cancers, both ovaries are always removed. This is called a bilateral oophorectomy. Oophorectomies are sometimes performed on pre-menopausal women who have estrogen-sensitive **breast cancer** in an effort to remove the main source of estrogen from their bodies. This procedure has become less common than it was in the 1990s. Today, **chemotherapy** drugs are available that alter the production of estrogen and **tamoxifen** blocks any of the effects any remaining estrogen may have on cancer cells.

Until the 1980s, women over age 40 having hysterectomies (surgical removal of the uterus) routinely had healthy ovaries and fallopian tubes removed at the same time. This operation is called a bilateral salpingo-oophorectomy. Many physicians reasoned that a woman over 40 was approaching menopause and soon her ovaries would stop secreting estrogen and releasing eggs. Removing the ovaries would eliminate the risk of ovarian cancer and only accelerate menopause by a few years.

In the 1990s, the thinking about routine oophorectomy began to change. The risk of ovarian cancer in women who have no family history of the disease is less than 1%. Meanwhile, removing the ovaries increases the risk of cardiovascular disease and accelerates osteoporosis unless a woman takes prescribed hormone replacements.

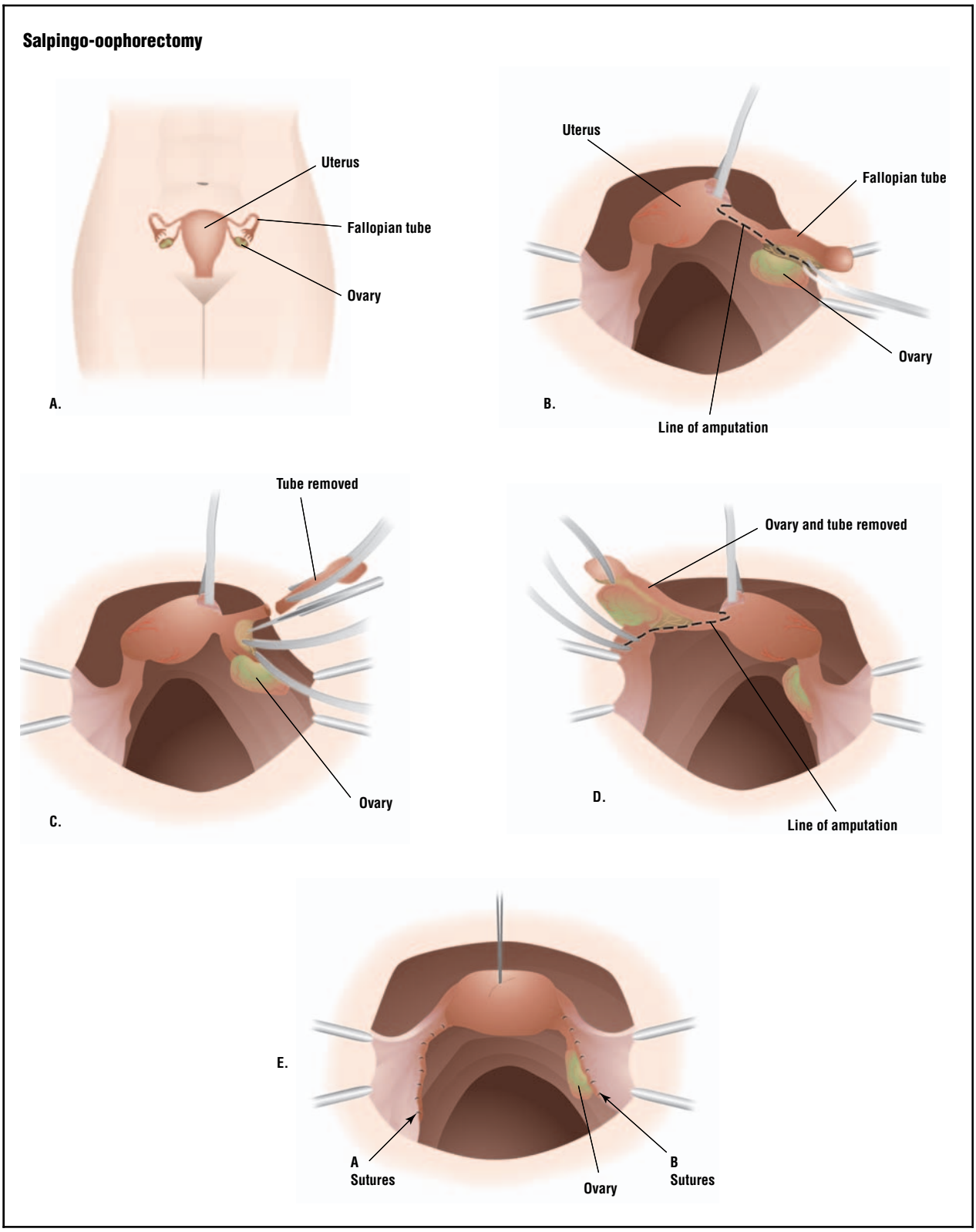
Under certain circumstances, oophorectomy may still be the treatment of choice to prevent breast and ovarian cancer in certain high-risk women. A study done at the University of Pennsylvania and released in 2000 showed that healthy women who carried the BRCA1 or BRCA2 genetic mutations that pre-disposed them to breast cancer had their risk of breast cancer drop from 80% to 19% when their ovaries were removed before age 40. Women between the ages of 40 and 50 showed less risk reduction, and there was no significant reduction of breast cancer risk in women over age 50.

Overall, ovarian cancer still ranks low on a woman's list of health concerns: It accounts for only 4% of all cancers in women. But the lifetime risk for developing ovarian cancer in women who have mutations in BRCA1 is significantly increased over the general population and may cause an ovarian cancer risk of 30% by age 60. For women at increased risk, oophorectomy may be considered after the age of 35 if childbearing is complete.

The value of ovary removal in preventing both breast and ovarian cancer has been documented. However, there are disagreements within the medical community about when and at what age this treatment should be offered. Preventative oophorectomy, called preventative bilateral oophorectomy (PBO), is not always covered by insurance. One study conducted in 2000 at the University of California at San Francisco found that only 20% of insurers paid for PBO. Another 25% had a policy against paying for the operation, and the remaining 55% said that they would decide about payment on an individual basis.

Precautions

There are situations in which oophorectomy is a medically wise choice for women who have a family



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history of breast or ovarian cancer. However, women with healthy ovaries who are undergoing hysterectomy for reasons other than cancer should discuss with their doctors the benefits and disadvantages of having their ovaries removed at the time of the hysterectomy.

Description

Oophorectomy is done under general anesthesia. It is performed through the same type of incision, either vertical or horizontal, as an abdominal hysterectomy. Horizontal incisions leave a less noticeable scar, but vertical incisions give the surgeon a better view of the abdominal cavity.

After the incision is made, the abdominal muscles are pulled apart, not cut, so that the surgeon can see the ovaries. Then the ovaries, and often the fallopian tubes, are removed.

Oophorectomy can sometimes be done with a laparoscopic procedure. With this surgery, a tube containing a tiny lens and light source is inserted through a small incision in the navel. A camera can be attached that allows the surgeon to see the abdominal cavity on a video monitor. When the ovaries are detached, they are removed though a small incision at the top of the vagina. The ovaries can also be cut into smaller sections and removed.

The advantages of abdominal incision are that the ovaries can be removed even if a woman has many adhesions from previous surgery. The surgeon gets a good view of the abdominal cavity and can check the surrounding tissue for disease. A vertical abdominal incision is mandatory if cancer is suspected. The disadvantages are that bleeding is more likely to be a complication of this type of operation. The operation is more painful than a laparoscopic operation and the recovery period is longer. A woman can expect to be in the hospital two to five days and will need three to six weeks to return to normal activities.

Preparation

Before surgery, the doctor will order blood and urine tests, and any additional tests such as ultrasound or x rays to help the surgeon visualize the woman's condition. The woman may also meet with the anesthesiologist to evaluate any special conditions that might affect the administration of anesthesia. A colon preparation may be done, if extensive surgery is anticipated.

On the evening before the operation, the woman should eat a light dinner, then take nothing by mouth, including water or other liquids, after midnight.

Aftercare

After surgery a woman will feel discomfort. The degree of discomfort varies and is generally greatest with abdominal incisions, because the abdominal muscles must be stretched out of the way so that the surgeon can reach the ovaries.

When both ovaries are removed, women who do not have cancer are started on hormone replacement therapy to ease the symptoms of menopause that occur because estrogen produced by the ovaries is no longer present. If even part of one ovary remains, it will produce enough estrogen that a woman will continue to menstruate, unless her uterus was removed in a hysterectomy. **Antibiotics** are given to reduce the risk of post-surgery infection.

Return to normal activities takes anywhere from two to six weeks, depending on the type of surgery. When women have cancer, chemotherapy or radiation are often given in addition to surgery. Some women have emotional trauma following an oophorectomy, and can benefit from counseling and support groups.

Risks

Oophorectomy is a relatively safe operation, although like all major surgery, it does carry some risks. These include unanticipated reaction to anesthesia, internal bleeding, blood clots, accidental damage to other organs, and post-surgery infection.

Complications after an oophorectomy include changes in sex drive, hot flashes, and other symptoms of menopause if both ovaries are removed. Women who have both ovaries removed and who do not take estrogen replacement therapy run an increased risk for cardiovascular disease and osteoporosis. Women with a history of psychological and emotional problems before an oophorectomy are more likely to experience psychological difficulties after the operation.

Normal results

If the surgery is successful, the ovaries will be removed without complication, and the underlying problem resolved. In the case of cancer, all the cancer will be removed.

Abnormal results

Complications may arise if the surgeon finds that cancer has spread to other places in the abdomen. If the cancer cannot be removed by surgery, it must be treated with chemotherapy and radiation.

KEY TERMS

Cyst—An abnormal sac containing fluid or semi-solid material.

Ectopic pregnancy—A pregnancy that develops when a fertilized egg implants outside the uterus, usually in the Fallopian tubes, but sometimes in the ovary itself.

Endometriosis—A benign condition that occurs when cells from the lining of the uterus begin growing outside the uterus.

Fallopian tubes—Slender tubes that carry ova from the ovaries to the uterus.

Hysterectomy—Surgical removal of the uterus.

Osteoporosis—The excessive loss of calcium from the bones, causing the bones to become fragile and break easily.

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American Cancer Society National Headquarters. 1599 Clifton Road NE, Atlanta, GA 30329. (800)ACS-2345. <http://www.cancer.org>.

Cancer Information Service, National Cancer Institute. Building 31, Room 10A19, 9000 Rockville Pike, Bethesda, MD 20892. (800)4-CANCER. <http://www.nci.nih.gov/cancerinfo/index.html>.

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Opioids

Definition

Opioids are narcotic drugs that are generally prescribed to manage pain. The most commonly prescribed opioids are: buprenorphine, butorphanol, codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, **meperidine**, methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, and propoxyphene. These opioids are prescribed alone or in combination with aspirin or acetaminophen (Tylenol).

The most common brand names for these drugs are:

- Actiq
- Astramorph PF
- Buprenex
- Cotanal-65
- Darvon
- Demerol
- Dilaudid
- Dolophine
- Duragesic
- Duramorph
- Hydrostat IR
- Kadian
- Levo-Dromoran
- Methadose
- M S Contin
- MSIR
- MS/L
- MS/S
- Nubain
- Numorphan
- OMS
- Oramorph SR
- OxyContin
- PP-Cap

- Rescudose
- RMS Uniserts
- Roxanol
- Roxicodone
- Stadol
- Talwin

When combined with aspirin or acetaminophen, the most common brand names are:

- Allay
- Anexsia
- Anolor
- Bancap-HC
- Capital with Codeine
- Co-Gesic
- Damason-P
- Darvocet
- Darvon
- DHCplus
- Dolacet
- Dolagesic
- Duocet
- E-Lor
- Empirin with codeine
- Endocet
- Endodan
- EZ III
- Hycomed
- Hyco-Pap
- Hydrocet
- Hydrogesic
- HY-PHEN
- Lorcet
- Lortab
- Margesic
- Oncet
- Panacet
- Panasal
- Panlor
- Percocet
- Percodan
- Phenaphen with codeine
- Polygesic
- Propacet
- Propoxyphene Compound-65
- Pyregesic-C
- Roxicet
- Roxilox
- Roxiprin
- Stagesic
- Synalgos-DC
- Talacen
- Talwin compound
- T-Gesic
- Tylenol with codeine
- Tylox
- Ugesic
- Vanacet
- Vendone
- Vicodin
- Vicoprofen
- Wygesic
- Zydone

Purpose

Opioids are primarily used to manage pain. Some narcotics are also used just prior to, or during, surgery to increase the effectiveness of certain anesthetics. Codeine and hydrocodone are used to relieve coughing. Methadone is used to help people control their dependence on heroine or other narcotics.

Description

Opioids act on the central nervous system (CNS) to relieve pain. Many of these drugs are habit-forming and physical dependence may lead to withdrawal side effects when the medication is stopped. Because of the potential habit-forming nature of these drugs, most prescriptions cannot be refilled and a new prescription must be obtained after each preceding prescription runs out.

Recommended dosage

Opioids may be taken either orally (in pill or liquid form), by injection (or as part of an intravenous [IV]. line), as an anal suppository, or as a patch attached to the

skin. The dosage prescribed may vary widely depending on the patient, the cancer being treated, and whether or not other medications are also being taken.

A typical adult dosage for buprenorphine is 0.3 mg injected into a muscle or vein every six hours as necessary. For children between the ages of two and twelve years, the dosage is typically 0.002 to 0.006 mg per kilogram (2.2 pounds) of body weight.

A typical adult dosage for butorphanol is 1-4 mg injected into a muscle or 0.5-2 mg injected into a vein every four hours as necessary. For children between the ages of two and twelve years, the dosage is typically based on the body weight of the child.

A typical adult dosage for codeine is 15-60 mg taken orally or injected into a muscle or vein every four to six hours as necessary for pain. This dosage is decreased to 10 to 20 mg when codeine is used to control coughing.

Fentanyl is most often used to manage pain in cancer patients who are already receiving and are tolerant to other opioids. This drug is available as a lozenge and as a skin patch. It is not used for the treatment of pain caused by injury or surgery. The dosage of fentanyl is determined on an individual patient basis by that patient's oncologist.

A typical adult dosage for hydrocodone is 5-10 mg taken orally every four to six hours as necessary for pain, 5 mg to control coughing.

A typical adult dosage for hydromorphone is 1-2 mg injected into a muscle, 2-2.5 mg taken orally, or 3 mg taken as a suppository every three to six hours as necessary.

A typical adult dosage for levorphanol is 2-4 mg taken orally or injected into a vein every four hours as necessary.

A typical adult dosage for meperidine is 100 mg taken orally or injected into a muscle or vein every four hours as necessary.

A typical adult dosage for methadone is 5-20 mg as an oral solution, 2.5-10 mg as an oral tablet or injection, every four to eight hours as necessary for pain. When used for detoxification, methadone is initially given in a dose of 15-40 mg per day as an oral solution. This dose is then decreased until the patient no longer requires the medication. The injection form of methadone is only used for detoxification in patients who are unable to take the medication by mouth.

Morphine is most often used to manage severe, chronic pain in patients who have already been receiving other narcotic pain relievers. The starting dose of morphine is generally determined based on the dosages of prior narcotic pain relievers the patient had been receiving. A typical starting dose is 5-30 mg every four hours.

100mg Demerol tablet. *(Copyright 2002 Thomson Micromedex. Reproduced by permission.)*

A typical adult dosage for nalbuphine is 10 mg injected into a muscle or vein every three to six hours as necessary.

A typical adult dosage for oxycodone is 5 mg taken orally every three to six hours, or 10-40 mg taken as a suppository three to four times per day as necessary.

A typical adult dosage for oxymorphone is 1-1.5 mg injected into a muscle every three to six hours, or 5 mg taken as a suppository every four to six hours as necessary.

A typical adult dosage for pentazocine is 50 mg taken orally, or 30 mg injected into a muscle or vein every three to four hours as necessary.

Propoxyphene comes in two salt forms: propoxyphene hydrochloride and propoxyphene napsylate. The typical adult dosage for propoxyphene hydrochloride is 65 mg taken orally every four hours with a maximum daily dosage of 390 mg. The typical adult dosage for propoxyphene napsylate is 100 mg taken orally every four hours with a maximum daily dosage of 600 mg.

Precautions

Opioids magnify the effects of alcohol and other central nervous system depressants, such as antihistamines, cold medicines, sedatives, tranquilizers, other prescription and over-the-counter pain medications, barbiturates, seizure medications, muscle relaxants, and certain anesthetics including some dental anesthetics. Alcohol and other central nervous system depressants should not be taken or consumed while opioids are being taken.

Opioids are powerful narcotics. These drugs can cause some people to feel drowsy, dizzy, or lightheaded. People taking opioids should not drive a car or operate machinery.

Opioids can be habit-forming. Patients who have been taking these types of medication for a period of several weeks should not stop taking this type of medication all at once. The dosage should be slowly tapered off to avoid potential withdrawal side effects.

Intentional or accidental overdose of any of the opioids can lead to unconsciousness, coma, or death. The signs of opioid overdose include confusion, difficulty speaking, seizures, severe nervousness or restlessness, severe dizziness, severe drowsiness, and/or slow or troubled breathing. These symptoms are increased by alcohol or other central nervous system depressants. Anyone who feels that he or she, or someone else, may have overdosed on opioids, or a combination of opioids and other central nervous system depressants, should seek emergency medical attention for that person at once.

Opioids can interfere with or exacerbate certain medical conditions. For these reasons, it is important that the prescribing physician is aware of any current case, or history of:

- alcohol abuse
- brain disease or head injury
- colitis
- drug dependency, particularly of narcotics
- emotional problems
- emphysema, asthma, or other chronic lung disease
- enlarged prostate
- gallstones or gallbladder disease
- heart disease
- kidney disease
- liver disease
- problems with urination
- seizures
- underactive thyroid

KEY TERMS

Central nervous system depressant—Any drug that tends to reduce the activity of the central nervous system. The major drug categories included in this classification are alcohol, anesthetics, antianxiety medications, antihistamines, antipsychotics, hypnotics, narcotics, sedatives, and tranquilizers.

Narcotic—Any drug that produces insensibility or stupor and/or generally causes effects similar to those caused by morphine.

Side effects

The most common side effects of opioids include:

- constipation
- dizziness
- drowsiness
- itching
- nausea
- urine retention
- vomiting

Less common side effects of opioids include:

- abnormally fast or slow heartbeat
- blurred or double vision
- cold, clammy skin
- depression or other mood changes
- dry mouth
- fainting
- hallucinations
- hives
- loss of appetite
- nightmares or unusual dreams
- pinpoint pupils of the eyes
- redness or flushing of the face
- restlessness
- rigid muscles
- ringing or buzzing in the ears

- seizure
- severe drowsiness
- skin reaction at the site of injection
- stomach cramps or pain
- sweating
- trouble sleeping (insomnia)
- yellowing of the skin or whites of the eyes

Interactions

Opioids should not be taken in combination with any prescription drug, over-the-counter drug, or herbal remedy without prior consultation with a physician. It is particularly important that the prescribing physician be aware of the use of any of the following drugs:

- carbamazepine (Tegretol; antiepileptic)
- central nervous system depressants
- monoamine oxidase (MAO) inhibitors (a class of antidepressants) such as furazolidone, isocarboxazid, pargyline, phenelzine, **procarbazine**, or tranylcypromine
- Naltrexone (opioid antagonist)
- Rifampin (antituberculosis drug)
- tricyclic antidepressants such as **amitriptyline**, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortiptyline, protriptyline, or trimipramine
- Zidovudine (antiviral against aids virus)
- any **radiation therapy** or **chemotherapy** medicines

Paul A. Johnson, Ed.M.

Opium tincture *see* **Antidiarrheal agents**

Oprelvekin

Definition

Oprelvekin, also known as Neumega, is a hematopoietic stimulant used as supportive care after myelosuppressive **chemotherapy** to combat thrombopenia.

Purpose

Oprelvekin is a prescription medication used following the administration of myelosuppressive chemotherapy drugs such as **azathioprine** and mercaptopurine. Myelosuppressive chemotherapy acts on bone marrow and causes a decrease in the amount of white blood cells (leukopenia) and platelets (thrombopenia). Oprelvekin acts as a growth factor stimulating stem cells to proliferate. The result is an increase in the amount of platelets (or thrombocytes).

Description

Oprelvekin is a recombinant human interleukin. Further it is a synthetic version of the naturally occurring interleukin-11, which is produced by the cells of the bone marrow. It is a growth factor that stimulates the formation of platelets, which are necessary in the process of blood clot formation. Oprelvekin is therefore important in increasing platelet formation after treatment with cancer medications that cause **thrombocytopenia**.

The Food and Drug Administration approve oprelvekin for prevention of severe thrombocytopenia, which is observed after chemotherapy. Oprelvekin is in **clinical trials** for treatment support and therapy for acute myelocytic leukemia.

Recommended dosage

This drug is available by injection. The dose is different from person to person and is dependent on the patient's body weight. Generally, 50 mcg/kg is given once daily in either the abdomen, thigh or hip. This medication should be taken at the same time every day for best results. If a dosage of oprelvekin is missed, the patient should skip the missed dose and take the next dose at the scheduled time.

Precautions

Although oprelvekin is effective at increasing the number of platelets in patients following chemotherapy, patients should understand that there are a number of precautions that should be taken when their physician is prescribing oprelvekin.

If the patient has any existing medical problems, he or she should tell the doctor prior to beginning treatment with oprelvekin. Congestive heart failure may be worsened when taking oprelvekin as it causes increased water retention. Oprelvekin can also cause atrial arrhythmias that result in heart rhythm problems. It should also be used with caution in patients with preexisting papilledema or with tumors that involve the central nervous system.

Oprelvekin has not been studied in pregnant women, women who are nursing or children. However, animal testing has shown that oprelvekin can have negative effects on the fetus and can cause joint and tendon problems in children. It is eliminated primarily by the kidneys and should be used carefully in patients with renal impairment.

KEY TERMS

Growth factor—A body-produced substance that regulates cell division and cell survival. It can also be produced in a laboratory for use in biological therapy.

Hematopoietic—Related to the formation of blood cells.

Thrombopenia—Decreased number of platelets.

Papilledema—Swelling around the optic disk.

Side effects

Although oprelvekin is a synthetic version of a naturally occurring growth factor, there are side effects associated with taking it. The side effects should be weighed against the needed effects of this medication. Some side effects do not require medical attention and others do.

The following are side effects that do not require medical attention and could gradually go away as treatment progresses:

- red eyes
- weakness
- numb extremities such as the hands and feet
- skin reactions such as rash and discoloration

If patients encounter any of the following side effects, they should contact their physicians immediately:

- rapid heartbeat
- irregular heartbeat
- short breath
- white spots in the mouth or on the tongue
- swelling feet and legs
- bloody eye
- blurred vision
- heart rhythm problems

If the patient notices any other side effects not listed, a physician should be contacted immediately.

Interactions

There are no known interactions with oprelvekin.

Sally C. McFarlane-Parrott

Oral cancers

Definition

Cancer of the mouth or the oral cavity and the oropharynx is referred to as oral cancer.

Description

Oral cavity describes a broad array of parts within the mouth including the lips, lining on the lips and cheeks referred to as buccal mucosa, teeth, tongue, floor of the mouth under the tongue, hard palate (which is the firm bony top of the mouth), and the gums. The oropharynx includes the back of the tongue, the soft palate, and the tonsils (fleshy part on either side of the mouth). There are glands through out the oral cavity that produce saliva that keep the mouth moist, known as salivary glands. The secretions from these glands called saliva aid in digesting the food.

Under normal circumstances, the oral cavity and oropharynx are comprised of several types of tissues and cells, and tumors can develop from any of these cells. These tumors may either be benign (they do not spread to the adjoining tissues), or the tumor may invade other tissues of the body. Any potential growth of a benign tumor into a cancerous (malignant) tumor is referred to as a precancerous condition. Leukoplakia or erythroplakia, which are abnormal areas in the oral cavity, may develop in many of the oral cancers as the first stage. Leukoplakia is a white area that is a benign condition, but approximately 5% of leukoplakias develop into cancer. Erythroplakia is a red bumpy area that bleeds when scraped, and has the potential to develop into cancer within 10 years if not treated.

Benign tumors are those that are not invasive and thus incapable of spreading. Examples of benign tumors of the oral cavity include keratocanthoma, leiomyoma, osteochondroma, neurofibroma, papilloma, schwannoma, and odontogenic tumors. These tumors are generally harmless and can be surgically removed. Recurrence of these tumors after surgical removal is very rare.

More than 90% of malignant tumors of the oral cavity and oropharynx are squamous cell carcinoma also referred to as squamous cell cancer. Squamous cells form the lining of the oral cavity and oropharynx and morphologically, they appear flat and scale-like. When the cancer cells appear just in the lining of the oral cavity, it marks the initial stages of the squamous cell cancer and is referred to as carcinoma in situ. Appearance of cancer cells on deeper layers of the oral cavity or oropharynx refers to invasive squamous cell cancer which is a more serious condition.

Verrucous carcinomas are a type of squamous cell carcinoma that seldom metastasize but can spread to the adjoining tissues. Thus a surgeon might suggest removal of a wide area of surrounding tissues in addition to removing the cancerous tissue. The chances of developing a second cancer in the oral region (oral cavity or pharynx) at a later time during the life period is about 10-40%, thus necessitating thorough follow-up examinations. In addition, refraining from smoking and drinking will help to prevent the disease recurrence. Among other types of malignant tumors of the oral cavity are salivary gland cancers and Hodgkin's disease. The former affects the salivary glands present throughout the mucosal lining of the oral cavity and oropharynx. The latter is the cancer that develops in the lymphoid tissue of the tonsils and base of the tongue.

Demographics

The statistical survey on oral cancers reveals that more men are affected by the disease than women. The American Cancer Society has estimated that about 28, 260 new cases of oral cavity and pharyngeal cancers will be diagnosed in the United States in the year 2004. Of these, predictions are that 18,550 cases will occur in men and 9,710 in women. The estimates also suggest that about 7,230 Americans will die of cancer of the oral cavity or oropharynx in 2004. The incidence and the mortality rate have been directed toward a decreasing trend in the last 20 years. Studies on patient survival show that about 82% of patients diagnosed with oral cancer survive for more than a year, about 51% survive for five years and about 48% for 10 years.

Certain geographic differences affect the incidence of oral cavity cancers. Hungary and France show higher incidence of the disease as compared to the United States. However, the disease is much less common in Japan and Mexico suggesting that environmental factors do play a key role in the outcome of the disease.

About 15% of patients diagnosed with either oral or oropharynx cancer are more often known to develop cancer of the adjoining organs (or tissues) including larynx, oesophagus or lung. The chances of developing a second cancer in the oral region (oral cavity or pharynx) for survivors, at a later time during the life period is about 10% to 40%. Thus, a person once diagnosed with cancer of oral cavity has to undergo through follow up examinations for the rest of his or her life, even if cured completely. In addition, restraining from smoking tobacco and drinking alcohol will greatly facilitate in preventing the disease occurrence as tobacco use has been shown to be responsible for 90% of tumors of oral cavity in men and 60% among women.

Causes and symptoms

The major risk factors for oral and oropharyngeal cancers are smoking and **alcohol consumption**. These two factors account for 75% of all the oral cavity cancers reported in the United States. Smokeless tobacco (chew or spit tobacco) is yet another important cause for oral cancers. Each dip or chew of tobacco has been shown to contain 5 times more nicotine than one cigarette and 28 potential carcinogens. For lip cancer, exposure to sun may be one of the risk factors. Geographical factors and sexual differences also attribute to the risk factors of oral cancers. Men are twice as susceptible to oral cancers than women. While oral cancer is ranked sixth leading cancer among men in the United States, it is the fourth leading cancer in African American men. Age also seems to be a factor in the susceptibility of oral cancer. About 95% of oral cancer cases are diagnosed in people older than 45 years and the median age for diagnosis is 64 years. In addition to these factors, genetic predisposition may be one of the factors that should not be ignored in any type of cancer.

Many of the symptoms listed below may be of a less serious nature or related to other cancers. Common symptoms include:

- mouth sores that do not heal
- persistent pain in the mouth
- thickening in the mouth
- white or red patch on tongue, gums, tonsils or lining of the mouth
- sore throat
- difficulty in chewing or swallowing
- difficulty moving the jaw or tongue
- numbness of gums, tongue or any other area of the mouth
- swelling of the jaw
- loosening of the teeth
- voice changes
- **weight loss**
- feeling of lumpy mass in the neck

Any of the above symptoms that persists for more than a few weeks needs prompt medical attention.

Diagnosis

Routine screening or examination of oral cavity by a physician or a dentist is the key for early detection of oral and oropharyngeal cancers. Thorough self-examination is also highly recommended by physicians that may lead to an early diagnosis of abnormal growth in the oral cavity

or neck. If any of the signs outlined above suggests the presence of oral cancer, the physician may recommend additional tests or procedures to confirm the diagnosis. These may be one or more of the following factors.

Head and neck examination

In addition to thorough physical examinations, physicians attach special attention to the neck and head area. Highly sophisticated fiberoptic scopes are used to view the oropharynx after inserting a tube through the mouth or nose. Because of the risk of additional cancers in patients with oral cancers, other parts of the head and neck including nose, larynx, lymph nodes are carefully examined. Depending on the parts examined, the procedures are termed as pharyngoscopy, **laryngoscopy** or nasopharyngoscopy.

Panendoscopy

Depending on the risk factors, the surgeon may suggest further examination of oral cavity, oropharynx, larynx, esophagus, trachea and the bronchi. This overall examination called panendoscopy is done under general anesthesia to avoid discomfort to the patient and allow a thorough check-up of the neck and head regions. During this process, a **biopsy** of the suspected tissue is done to determine the severity of the cancer. The specimens used could be a scraping from the suspected area and smeared into a slide which is stained and viewed under the microscope. This technique is easy, inexpensive and offers information on the abnormal lesions. Incisional biopsy is the removal of a piece of small tissue from an area of the tumor. This is a relatively simple procedure and is performed either in the doctor's office or in the operating room depending upon the area of the tumor to be removed. The biopsy tissue samples are treated through various steps before the cells can be viewed under the microscope. Fine-needle aspiration (FNA) biopsy is the aspiration of fluid from a mass, lump or cyst in the neck. This would also include excisional biopsy. Depending upon the type of cells recognized in the aspiration, the pathologists can determine whether the cancer is related to neck or oral region or it has metastasized from a distant organ. FNA may also determine whether the neck mass is benign that resulted from any infection related to mouth or oropharynx.

Computed tomography (or Computer Axial tomography)

A sophisticated x-ray test that scans parts of body in cross-section. This procedure is carried out after administering a dye that can aid in locating abnormalities. This helps in judging the extent of cancer spread to lymph nodes, lower mandible and neck.

Magnetic resonance imaging (MRI)

This is used for evaluting soft tissue details such as the cancers of the tonsil and base of tongue and the procedure is governed by magnets and radio waves.

Panorex

This is a rotating **x ray** of upper and lower jawbones that determines changes that occur due to cancers in the oral cavity.

In addition to the imaging tests already noted, chest x rays help in checking for lung cancers in oral cancer patients with smoking habits. Barium swallow is a commonly performed series of x rays to assess the cancers of the digestive tract in patients with oral cancer. A radionulide bone scan may be suggested if there is concern that the cancer may have spread to the bones.

Other tests may include blood tests given to provide a complete blood analysis, including a determination of **anemia**, liver disease, kidney disease and RBC and WBC counts.

Treatment team

Cancer care team typically involves physician specialists to include, surgeon (oral or neck and head surgeon), a dentist (in cases of oral cancers), a medical oncologist and a radiation therapist.

Clinical staging, treatments, and prognosis

Clinical staging

TNM system of the American Joint Committee on Cancer has been followed in staging the cancer in which the size (T), spread to regional lymph nodes (N) and **Metastasis** to other organs (M) are classified.

T CLASSIFICATION

- Tx: Information not known and thus tumor cannot be assessed.
- T0: No evidence of primary tumor.
- Tis: Carcinoma in situ which means the cancer has affected the epithelial cells lining the oral cavity or the oropharynx and the tumor is not deep.
- T1: Tumor 2 cm (1 cm equals 0.39 inches) or smaller.
- T2: Tumor larger than 2 cm but smaller than 4 cm.
- T3:Tumor larger than 4 cm.
- T4: Tumor of any size that invades adjacent structures like larynx, bone, connective tissues or muscles.

N CLASSIFICATION

- Nx: Information not known, cannot be assessed.
- N0: No metastasis in the regional lymph node.
- N1: Metastasis in one lymph node on the same side of the primary tumor and smaller than 3cm.
- N2: Divided into 3 subgroups. N2a is metastasis in one lymph node larger than 3cm and smaller than 6cm. N2b is metastasis in multiple lymph nodes on the same side of tumor, none larger than 6cm. N2c denotes one or more lymph nodes, may or may not be on the side of primary tumor, none larger than 6 cm.
- N3: Metastasis in lymph node larger than 6cm.

M CLASSIFICATION

- Mx: Distant metastasis cannot be assessed, information not known.
- M0: No distant metastasis.
- M1: Distant metastasis present.

STAGE GROUPING

- Stage 0 (carcinoma in situ): Tis,N0,M0
- StageI: T1,N0,M0
- Stage II: T2,N0,M0
- Stage III: T3,N0,M0 or T1,N1,M0 or T2,N1,M0 or T3,N1,M0
- Stage IVA: T4,N0,M0 or T4,N1,M0 or Any T,N2,M0
- Stage IVB: Any T,N3,M0
- Stage IVC: Any T, any N,M1

Treatments

After the cancer is diagnosed and staged, the medical team dealing with the case will discuss the choice of treatment. This may be **chemotherapy** alone or in combination with **radiation therapy** or surgery. The treatment option is made depending upon the stage of the disease, the physical health of the patient, and after discussing the possible impact of the treatment on speech, swallowing, chewing, or general appearance.

SURGERY Primary tumor resection involves removal of the entire tumor with some normal adjacent tissue surrounding the tumor to ensure that all of the residual cancerous mass is removed. Partial mandible resection is carried out in cases where the jaw bone is suspected to have been invaded but with no evidence from x ray results. Full mandible resection is performed when the x rays indicate jaw bone destruction.

Maxillectomy is the removal of the hard palate if that is affected. A special denture called a prosthesis can alter the defect caused in the hard palate resulting from the surgery. Moh's surgery involves removal of thin sections of lip tumors. Immediate examination of the sections for potential cancer cells allows the surgeons to decide whether or not the cancer is completely removed.

Laryngectomy is the surgical removal of larynx (voice box). This is done when there is risk of food entering the trachea and infecting the lungs, as a result of removal of tumors of tongue or oropharynx. By removing the larynx, the trachea is attached to the skin of the neck thus eliminating the risk of infecting the lung and potential **pneumonia**.

Neck dissection is a surgical procedure involving removal of lymph nodes in the neck that are known to contain cancer cells. The side effects of this surgery include numbness of the ear, difficulty in raising the arm above the head, discomfort to the lower lip—all of which are caused by different nerves involved in the surgery.

Tracheostomy is an incision made in the trachea to facilitate breathing for oral cancer patients who may develop considerable swelling following surgical removal of the tumor in oral cavity. This prevents any obstruction in the throat and allows easy breathing.

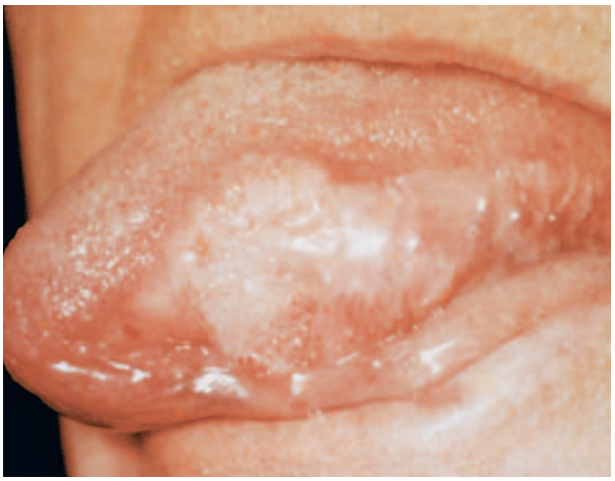
In addition to the those surgical procedures, dental extractions and removal of large tumors in oral cancer patients may need reconstructive surgeries which may vary from one patient to the other depending upon the site and size of the tumors.

RADIATION THERAPY Use of high-energy rays to kill the cancer cells or reduce their growth is radiation therapy. It may be given as the only treatment of small tumors or given in combination with surgery to destroy deposits of cancer cells. Radiation is also suggested for relieving symptoms of cancer including difficulty in

KEY TERMS

Biopsy—Removal of a portion of tissue or cells for microscopic examination. Incisional biopsy is removal of only a sample tissue. Excisional biopsy is removal of entire tumor or lesion. Sample of tissue or fluid removed with a needle is fine-needle biopsy.

Lymph node—Bean-shaped mass of lymphatic tissue surrounded by connective tissue. These contain lymphocytes which are cells that helps in maintaining the immune system.



Close-up of large cancerous tumor on the tongue. *(Copyright Biophoto Associates, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

swallowing and bleeding. Radiation may be externally or internally administered. External radiation (also called external beam radiation therapy) delivers radiation to oral or oropharyngeal cancers from outside the body. Brachytherapy or internal radiation involves the surgical implant of metal rods that deliver radioactive materials in or near the cancer.

CHEMOTHERAPY Chemotherapy involves administering of anticancer drugs parenterally or orally. Chemotherapy may be suggested in combination with radiation therapy to avoid surgery in some large tumors of head and neck region. Some studies reveal that chemotherapy is ideal for shrinking the size of the tumor before surgery or radiation therapy is initiated. This is termed neoadjuvant chemotherapy.

Treatment choices by stage and prognosis

Depending on the stage of cancer spread, different treatment options are recommended for oral cancer.

Stage 0: Surgical stripping or thin resection is suggested at this stage where the cancer has not become invasive. If there is repeated recurrence, radiation therapy is an option. More than 95% of the patients at this stage survive for long-term without the requirement of any surgery of their oral cavity.

Stages I and II: Surgery or radiation therapy is the choice of treatment depending on the location of the tumor in the oral cavity and oropharynx.

Stages III and IV: A combination therapy of either surgery and radiation or radiation and chemotherapy or all the three types of treatment may be required for these advanced stages of cancer. About 20% to 50% of patients undergoing a combination of surgery and radiation for stages III and IV oral cavity and oropharyngeal cancers have the chances of five-year disease-free survival.

Alternative and complementary therapies

Various alternative medications are being tried periodically. While choosing any alternative therapy, a thorough discussion of the advantages and disadvantages of the suggested therapy with the medical team is highly recommended.

As of 2000, researchers had demonstrated that Bowman-Birk inhibitor, a protein found in soybeans shrinks leukoplakia or the precancerous growth in the mouth. The study has pointed to a reduction in the size of the leukoplakia to a third or half of the original size when the protein is orally administered for a month. The studies also suggest that a combination of soybean intake and termination of smoking tobacco will have a cumulative effect in the shrinking of leukoplakia. However, a thorough investigations in a larger patient population is necessary to confirm the therapeutic utility of the soybean protein in oral cancer.

Coping with cancer treatment

Cancer of any type is a psychologically distressful journey from the time of diagnosis, treatment and recovery. Coping with the side effects of treatment both physically and emotionally is a challenge to the patient, the family and the medical team. Oral cancers are further complicated by the fact that surgery most often leads to disfigurement which may be devastating in a society where importance is attached to physical appearance. Reconstruction surgeries or facial prostheses may be psychologically helpful and the cancer care team may advise on this issue. Laryngectomy or removal of the voice box leaves the person without speech, and breathing through stoma (in the neck). A stoma cover helps in hiding the mucus that the stoma secretes and also serves as a filter in the absence of nose's natural filter. The odors from the stoma can be prevented by use of cologne, and by avoiding strongly scented foods such as garlic. Studies reveal that lack of normal speech has a serious impact on sexual activity in couples. In addition to laryngectomy, surgery on the jaw, plate or tongue can also disrupt speech. These problems need to be discussed with the cancer care team or contact organizations such as the American Cancer Society who could provide relevant information on coping with specific issues on oral cancers.

Side effects of chemotherapy such as **fatigue** and hair loss (alopecia) may affect the quality of life in a

patient. A wig may be used for cosmetic purposes that can hide the hair loss. Studies have shown that patients may gradually regain their health after chemotherapy if they abstain from smoking and drinking.

Clinical trials

Evaluation of a potential treatment method for a disease on aselected patient population is called a clinical trial. Some of the ongoing **clinical trials** include:

- Paclitaxel and cisplatin for Stage III and IV of squamous cell carcinoma of the oral cavity following radiotherapy.
- Phase I study of intratumoral EGFR antisense DNA and DC chol liposomes in patients with advanced squamous cell carcinoma of oral cavity.
- Phase I immunotoxin therapy (PE38 immunotoxin) in treating patients with advanced lip and oral cavity cancer.
- Phase III megestrol acetate administration to patients undergoing cancer treatment for lip, oral cavity, and oropharyngeal cancers. This drug improves appetite and thus may prevent weight loss in cancer patients.
- Phase I combination of chemotherapy and radiation therapy in treating Stage III/IV lip, oral cavity, and **oropharyngeal cancer**. The drug tested is docetaxel.

Resources regarding these clinical trials, as well as many others regarding oral cancers, including any recruiting of patients for the trial are available at <Clinical Trials.gov.> which is a service of the National Cancer Institute, National Institutes of Health.

Prevention

Oral cavity and oropharyngeal cancer patients are at risk for recurrences, or for developing secondary cancers in the head and neck area. Thus a close follow-up is mandatory in the first couple of years following the indicence. A thorough examination every month in the first year, and at least every three months during the following year, and each year thereafter is the recommended schedule to facilitate early detection, if any. Various chemopreventive drugs are being tested to prevent the occurrence of secondary tumors in the neck and head region. Vitamin A analog is one such chemopreventive drug under investigation that may help in suppressing the tumor formation.

Tobacco (smoking, chewing, spitting) and alcohol consumption are the major causes of oral and oropharyngeal cancers. Public knowledge regarding the risk factors of the oral cancers and the signs of early detection is limited. Only 25% of U.S. adults can detect early signs of abnormal oral cavity; and only13% understand the implications of regular alcohol consumption in developing oral cancer. **Cancer prevention** and control programs are growing rapidly with screening services for high risk opulation, health promotion, education and intervention strategies. National Spit Tobacco Education Program (NSTEP), an initiative of Oral Health America, has been educating the public about dangers of spit tobacco and oral cancer.

Exposure to sun may cause **lip cancers**. Use of a lip balm will protect the lip from the sun rays. In addition, pipe smokers are more at risk for lip cancers.

QUESTIONS TO ASK THE DOCTOR

- What is oral cavity or oropharyngeal cancer?
- What is the extent of cancer spread beyond the primary site?
- What is the stage, and the severity of the stage?
- What are the treatment options available?
- What are the chances of survival,and the time frame of survival?
- What are the side of effects of treatment?
- What are the potential risks of specific treatments?
- How long will it take to recover from treatment?
- What are the chances of recurrence?
- What is the benefit of one treatment over the other in terms of recurrence?
- How to get ready for the treatment?
- Discuss the possibility of getting a second opinion.

Special concerns

Surgery for oral cancer treatment may affect normal speech and swallowing. A speech pathologist will educate, and suggest remedies for restoring speech and swallowing problems. In addition, a dietitian may be consulted for choosing the more palatable food in the advent of chewing and swallowing problems. In case of dryness, a saliva supplement can be recommended by a physician.

Advances in reconstructive surgery of the mouth and lower face in the early 2000s have significantly improved patients' appearance and quality of life after treatment for oral cancer.

The side effects of cancer treatment will make the patient fatiqued. Giving ample time to recover will help improve energy for the long-term. **Smoking cessation** and elimination of alcohol, and maintaining a balanced diet with fruits, vegetables, and whole grain are key to returning to a normal life for patients suffering from oral cancers.

See also Cancer biology; Cancer genetics; Cigarettes.

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Orbital exenteration and Pelvic exenteration

see **Exenteration**

Orchiectomy

Definition

Orchiectomy is a surgical procedure to remove one or both testes in men with prostate or **testicular cancer**. The procedure is sometimes called orchidectomy.

Purpose

In men who have **prostate cancer**, an orchiectomy, up until the 1990s, was considered the standard treatment. By removal of the testes, the influence of **testosterone**, the male hormone produced by the testes, is removed. Testosterone stimulates prostate cancer growth and progression of the disease.

Orchiectomy is done in men with testicular cancer to remove one or both testes that have cancer. By removing the cancerous testes, there will then be zero chance that the cancer can recur in the testes.

In children or in younger men, the surgeon may perform what is known as testis-sparing or testicular-sparing surgery, in which only the tumor is removed while the healthy testicular tissue is allowed to remain. According to one Canadian study of 51 boys between infancy and 16 years of age, testicular-sparing surgery is highly successful with regard to cancer control as well as tissue preservation.

Precautions

The orchiectomy operation is generally a very basic and safe operation. As in any surgery, some bleeding will be expected, so men should not be taking any medications like aspirin or ibuprofen that could decrease their blood's ability to clot.

Description

An orchiectomy usually takes place in a hospital setting, either in an outpatient surgery clinic or in the hospital itself. General presurgery procedures, such as

blood work, are done a few days to a week before the procedure.

To ensure that a patient having an orchiectomy does not suffer any pain, anesthetic will be used during the procedure. Generally, two types of anesthetic are used during an orchiectomy: general anesthesia and epidural anesthesia. General anesthesia causes the patient to go into a sleeplike state. With epidural anesthesia, the patient is awake but is totally numb from the waist down and therefore cannot feel the operation.

Once the patient is adequately anesthetized, the surgeon will make a four-inch incision through the lower abdomen. After the incision in the lower abdomen is made, the surgeon will gently push the testicles up through the inguinal canal and out through the incision.

The orchiectomy operation generally takes only 45 minutes to an hour. Patients either stay overnight in the hospital or are discharged from the hospital the same day if there appear to be no complications. Pain from the surgery is usually mild to moderate; narcotic pain medications can control the pain for most patients.

Preparation

There are no specific preparations for having an orchiectomy versus any other type of surgery. Blood will be taken before the surgery to check for infections or other contraindications to surgery. Patients are also advised not to take any medications such as aspirin or ibuprofen that may interfere with the blood's clotting ability.

Aftercare

For approximately two to four weeks or even longer, patients are advised not to participate in any strenuous physical activity. Pain in the scrotum and abdominal area may persist for days to weeks. The surgical wound site should be kept clean and dry. It should also be watched for any signs of infection, such as an increase in pain, unusual redness or swelling, or a foul-smelling discharge.

Risks

The risks of orchiectomy include such general surgical risks as pain, bleeding, and infection. In rare cases more serious complications could develop, including abscess formation and bladder damage.

Normal results

The goal of an orchiectomy is to remove the testicles without undue damage to any other organs or structures. For testicular cancer, the end result is to remove the cancerous testicle and cure the cancer. For prostate cancer,

KEY TERMS

Inguinal canal— A pair of internal openings that connect the abdominal cavity with the scrotum in the male fetus, allowing for the developing testes to descend into the scrotal sac.

Testes— The male sex organs that produce sperm and male sex hormones.

the end result is to remove the testicles to shut down the synthesis of testosterone, which is known to promote prostate cancer growth.

Abnormal results

Abnormal results of an orchiectomy can include incomplete removal of the testicles. In the case of both testicular cancer and prostate cancer, this could result in the progression of the cancer.

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Oropharyngeal cancer

Definition

Oropharyngeal cancer is an uncontrolled growth of cells that begins in the oropharynx, the area at the back of the mouth.

Description

The oropharynx is the passageway at the back of the mouth. It connects the mouth to the esophagus (tube through which food passes) and to the pharynx (the channel for the flow of air into and out of the lungs). It takes its name from the way it ties the oral cavity (hence the oro) to the rest of the pharynx, one part of which extends toward the back of the nose (nasopharynx). The base of the tongue, the soft palate (the soft roof of the mouth, above the base of the tongue) and the tonsils are part of the oropharynx.

If the oropharynx is blocked or injured in any way, the condition presents a threat to life because it interferes with both eating and breathing. Thus, an obstruction caused by oropharyngeal cancer is in itself a problem. Oropharyngeal cancer also contributes to problems with chewing and talking because of the importance of the oropharynx in these activities. If the oropharyngeal cancer spreads to the bone, muscle, and soft tissue in the neck, there is a severe effect on the ability of the neck to support the head. In individuals with oropharyngeal cancer that has spread, surgical options might be limited.

Oropharyngeal cancer usually begins in the squamous cells of the epithelial tissue. The squamous cells are flat, and often layered. The epithelial tissue forms coverings for the surfaces of the body. Skin, for example, has an outer layer of epithelial tissue. Throughout the oropharynx there are some very small salivary glands and one of more of them sometimes becomes the site of tumor growth.

Many times cancer that begins in the oropharynx spreads to the base of the tongue. Oropharyngeal cancer can spread to the muscle and bone in the neck, and also to the soft tissue that fills the space around the muscle and bone.

Demographics

In the United States, about 4,000 cases of oropharyngeal cancer are diagnosed each year. Most of the cancer is found in people who are more than 50 years old. A history of tobacco or alcohol use, especially heavy use, is typically linked to the diagnosis. Men are three to five times more likely to be diagnosed than women.

Some benign tumors arise in the oropharynx. Although they are benign, many studies suggest the growths indicate the person is at greater risk for a malignant tumor growth in the future.

Causes and symptoms

The cause of oropharyngeal cancer is not known, but the risk factors for oropharyngeal cancer are understood. Three important lifestyle choices increase the chance a person will be diagnosed with cancer of the oropharynx. They are tobacco use, alcohol consumption, and certain sexual practices.

Anything that passes into the lungs or stomach through the nose and mouth must move through the oropharynx. (Air moves through the nasopharynx to reach the oropharynx.) Long periods of exposure to substances such as tobacco byproducts and alcohol somehow trigger cells to begin uncontrolled growth, cancer. About 90 percent of all cancer of the oropharynx starts in a squamous cell.

Since tobacco and alcohol come into direct contact with the squamous cells of the oropharynx as they move through the cavity, they might change the genetic material (DNA) of cells. If a cell cannot repair damage to DNA, a cancerous growth can begin.

A serious interaction occurs between tobacco and alcohol. Individuals who smoke and drink alcoholic beverages are at much greater risk for oropharyngeal cancer. They have as much as 30 times or 40 times the normal risk. The estimate is difficult to make because not all individuals diagnosed are accurate in the statements they make to physicians about their use of these substances. Patients often say they used less tobacco or less alcohol than they actually did.

Viral infection increases the risk of oropharyngeal cancer. So does reduced immunity, which is a condition that may be caused by viral infection. Individuals with human papilloma viruses, which are sexually transmitted, are known, as of 2004, to be at greater risk, particularly those infected by HPV-16. The virus increases a person's risk of cancer because it inactivates the TP53 gene, which regulates the cycle of cell division by keeping cells from dividing in an uncontrolled fashion. The specific sexual practices associated with an increased risk of oropharyngeal cancer include a high lifetime number of sexual partners, oral-gential sex, and oral-anal sex.

Marijuana seems to be linked with oropharyngeal cancer too. Vitamin A deficiency, or specifically, the absence of the carotene (from fruits and vegetables) that the body uses to make vitamin A, might also be a contributing factor.

Symptoms of oropharyngeal cancer include:

- difficulty swallowing
- difficulty chewing
- change in voice
- loss of weight
- lump in the throat
- lump in the neck

Diagnosis

Cells grow old and flake off regularly from epithelial tissues. The first step in diagnosing oropharyngeal cancer often makes use of the natural process. It is given the name exfoliative **cytology**. A physician scrapes cells from the part of the oropharynx where a cancer is suspected and smears them on a slide. The cells are then treated with chemicals so they can be studied with a microscope. If they do not appear normal, a **biopsy**, or a tissue sample from a deeper layer of cells, is taken for examination.

Different sorts of biopsies are used. An incision, or cut, is be made to obtain tissue. Or, a needle with a small diameter is inserted into the neck to obtain cells, especially if there is a lump in the neck.

Computed tomography (CT) and **magnetic resonance imaging** (MRI) scans are also used. They help determine whether the cancer has spread from the walls of the oropharynx. MRI offers a good way to examine the tonsils and the back of the tongue, which are soft tissues. CT is used as a way of studying the jaw, which is bone.

Many extremely specialized means of determining the condition of the oropharynx have been developed. One of them relies on the same sort of light wave technology that now powers much of the communications world, fiberoptics. A fiber (a bundle of glass fibers, actually) with a very small diameter is inserted in the oropharynx and the area is probed with light that is reflected on mirrors for interpretation. Lighting up the oropharynx with the high intensity, very low heat illumination of fiberoptics, a physician can get a good look at the cavity.

Another special way of getting a good look at the oropharynx involves studying it from within by inserting an endoscope into the oropharynx and then, weaving it through adjacent connecting structures. The structures include the trachea, the bronchi, the larynx and the esophagus. The patient is given an anesthetic, local or general, for this procedure. When several organs are examined at the same time, the procedure is called a

panendoscopy. The tool used is generally named for the organ for which it is most closely designed. For example, there is a laryngoscope.

Because oropharyngeal cancer often spreads, bones near the oropharynx must be examined carefully. Some special types of equipment are used. A rotating **x ray** called panorex provides for close inspection of the jaw.

Oropharyngeal cancer also spreads to the esophagus, so physicians usually examine the esophagus when they diagnose oropharyngeal cancer. To do so, they ask the patient to drink a liquid containing barium, a chemical that can be seen on x rays. Then, they can x ray the esophagus and look for bulges or lumps that indicate cancer there.

Treatment team

Generally, physicians with special training in the organs of the throat take responsibility for the care of a patient with oropharyngeal cancer. They are called otolaryngologists or occasionally by a longer name, otorhinolaryngologists.

In abbreviation, otolaryngologists are usually labeled ENT (for Ear, Nose and Throat) specialists. An ENT specializing in cancer will probably lead the team. Some ENTs have a specialty in surgery. Some have a specialty in oncology. Some have a specialty in both.

Nurses, as well as a nutritionist, speech therapist and social worker will also be part of the team. Depending on the extent of the cancer when diagnosed, some surgery and treatments result in extensive changes in the throat, neck and jaw. The social worker, speech therapist and nutritionist are important in helping the patient cope with the changes caused by surgery and radiation treatment. If there is great alteration to the neck because of surgery, rehabilitation will also be part of the recovery process and a rehabilitation therapist will be added to the team.

The treatment team may also include a psychiatrist, as patients with oropharyngeal cancer have extremely high rates of depression compared with other cancer patients. A study carried out at Memorial Sloan-Kettering Cancer Center in New York reported in 2004 that as many as 57% of patients with oropharyngeal cancer suffer an episode of major depression, compared to 50% of pancreatic cancer patients, 46% of breast cancer patients, and 44% of lung cancer patients.

Clinical staging, treatments, and prognosis

Stage 0 indicates some cells with the potential to grow erratically are discovered. But the cells have not multiplied beyond the surface layer of the epithelial tissue of the oropharynx. Stage I describes a cancer less than approximately 2.5 cm (about one inch in diameter) that has not spread. Stage II describes a bigger cancer, up to about 5 cm. (about two inches), that has not spread.

Stage III oropharyngeal cancer is either larger than two inches or has spread to one lymph node. The lymph node is enlarged but not much larger than an inch.

In Stage IV, one or more of several things happens. There is either a spread of cancer to a site near the original site. Or, there is more than one lymph node with cancer. Or, the cancer has spread to other parts of the body, such as the larynx, the trachea, the bronchi, the esophagus, or even more distant points, such as the lungs.

The outlook for recovery from oropharyngeal cancer is better the earlier the stage in which the cancer is diagnosed. For stage I and stage II, surgical removal or radiation therapy of the affected area is sometimes all that is required to halt the cell growth. Decisions about which method to use depend on many factors. The tolerance a patient has for radiation or **chemotherapy**, and the size of the tumor are crucial to the decision process.

Surgical removal can interfere with speech, eating and breathing. So, if nonsurgical treatment is an option, it is a good one to try. The larger the tumor, the more urgent is its removal. Smaller tumors can be treated with radiation or chemotherapy to shrink them before surgery. Some smaller tumors can be removed completely with a carbon dioxide laser. In some cases, surgery might be avoided. For stage III cancer with lymph node involvement, the lymph nodes with the cancer are also removed.

Chemotherapy might be used at any stage, but it is particularly important for stage IV cancer. In some cases, chemotherapy is used before surgery, just as radiation is, to try to eliminate the cancer without cutting, or at least to make it smaller before it is cut out (excised). After surgery, **radiation therapy** and chemotherapy are both used to treat patients with stage IV oropharyngeal cancer, sometimes in combination. Treatments vary in Stage IV patients depending on the extent of the spread.

Some tumors are so large they cannot be completely removed by surgery. Often, the most promising treatment option for a person with such a tumor is a clinical trial. One technique that has had some success with recurrent or advanced oropharyngeal tumors is radiofrequency ablation. In radiofrequency ablation, the tumor is heated by the application of 90–150 watts of energy to an internal temperature of 60–110°C (140–230°F) for a period of 5–15 minutes.

Besides categories, or stages, that indicate how far the disease has progressed, there are many categories that are used to describe the kind, or grade, of tumor. The

grades take into account such factors as the density of a tumor. Eventually, physicians hope information about tumor grade will make it possible to match treatment and condition very precisely.

Coping with cancer treatment

The patient should be an active member of the treatment team, listening to information and making decisions about which course of treatment to take. Premier cancer centers encourage such a role.

Prior to surgery, discuss the need for a way to communicate if speech is impaired after surgery. A pad and pencil might be all that are needed for a short interval. If there will be a long period of difficulty, the patient should be ready with other means, including special phone service.

A change in appearance after the removal of part of the oropharynx, whether part of the tongue or soft palate or some other portion, can lead to concerns about **body image**. Social interaction might suffer. A support group can help. Discussions with a social worker also can be beneficial.

If any part of the oropharynx is removed, speech therapy might be necessary to relearn how to make certain sounds. If the surgery requires the removal of some or all of the tongue, a person's speech will be greatly impaired.

Appetite might be affected before, during and after treatment. Before treatment, the presence of a tumor can interfere with chewing and swallowing food, and food might not seem as appealing as it once did. During treatment, particularly radiation treatment, the treated oropharynx will be sore and eating and breathing will be difficult, or impossible.

In some cases, a patient requires a feeding tube (inserted at the opening of the esophagus, through the mouth), a stomach tube (inserted directly in the stomach, if there is no access to the opening of the esophagus) or a breathing tube (inserted directly in the trachea) for some interval of time. The tubes bypass the normal entryways to the stomach and lungs. Liquid food is put directly into the esophagus or stomach. Air is taken directly into the trachea during breathing. The incision or cut in the trachea is called a tracheotomy and the opening in the neck around the trachea is a tracheostomy. Air that enters the trachea directly is not warmed or moistened, and the dry, cold air in the lungs can lead to respiratory complications. Attachments are now available that are positioned at the opening in the neck and filter and add moisture to the air entering the tracheal tube. Learning how to care for the tracheotomy and tracheostomy, how to keep the openings clean and what to do if the tube pops out, relieves anxiety and improves ease of breathing.

After treatment, a loss of sensation in the part of the oropharynx affected, or a loss of part of the tongue or the jaw, can reduce appetite. A nutritionist can help with supplements for people who experience significant **weight loss** and who do not have an appetite (anorexia).

Patients who are dependent on tobacco or alcohol products and want to reduce or eliminate their intake, will have to deal with the psychological effects of substance withdrawal in addition to the side-effects from treatment. A support group for tobacco or alcohol dependence might be considered, and joined before treatment begins.

Clinical trials

There are a number of **clinical trials** in progress. For example, the better researchers understand the nature of cancer cells, the better they are able to design drugs that attack only cancer cells. Or, in some cases, drugs that make it easier to kill cancer cells have also been designed.

The Cancer Information Service at the National Institutes of Health, Bethesda, Md., offers information about clinical trials that are looking for volunteers. The Service offers a toll-free number at 1-800-422-6237.

Prevention

Avoiding smoking, drinking alcohol, and having oral sex with a large number of partners are important in the prevention of oropharyngeal cancer. Including lots of fruits and vegetables in the diet is also an important step to preventing cancer. (Even though the importance of fruits and vegetables is not proven to prevent oropharyngeal cancer, overall fruits and vegetables are demonstrated cancer fighters.) Carotene, which the body uses to make vitamin A, seems to be important in the diet of people who are less likely to be diagnosed with oropharyngeal cancer. Any precaution that is taken to avoid contracting sexually transmitted diseases, such as the use of condoms, also offers protection from oropharyngeal cancer.

Special concerns

Growths sometimes develop in the oropharynx that are not cancerous. The benign tumors can be removed by surgery. They usually do not recur. The surgeon should be able to give a patient an accurate appraisal identifying the noncancerous growth, and whether it is likely to indicate future problems.

KEY TERMS

Biopsy—Tissue sample is taken from body for examination.

Bronchi—Branches of the trachea that distribute air to the air sacs (alveoli) of the lungs.

Computed tomography (CT)—X rays are aimed at slices of the body (by rotating equipment) and results are assembled with a computer to give a three-dimensional picture of a structure.

Endoscope—Instrument designed to allow direct visual inspection of body cavities, a sort of microscope in a long access tube.

Fiberoptics—Cool, refracted (bounced) light passes (bounces) along extremely small diameter glass tubes. (Used to illuminate body cavities, such as the oropharynx, with high intensity, and almost heatless light.)

Larynx—Commonly known as the voice box, the place between the pharynx and the trachea where the vocal cords are located.

Magnetic resonance imaging (MRI)—Magnetic fields and radio frequency waves are used to take pictures of the inside of the body.

Salivary glands—Structures in the mouth that make and release (secrete) saliva that helps with digestion.

Tonsils—Lymph nodes in the throat that are partly encapsulated (enclosed). They are components of the lymphatic system that functions in immunity and removes the excess fluid around cells and returns it to cells.

Trachea—Tube ringed with cartilage that connects the larynx with the bronchi.

Oropharyngeal cancer frequently recurs in patients who have been treated for the condition. Thus, after treatment, patients must be examined monthly for one year. They also must be committed to telling their physician if they notice any changes. By the second year, examinations can be at two-month intervals; and then, three-month intervals by the third year and six-month intervals beyond that.

Mouthwash has been suspected as a cancer-causing agent for oropharyngeal cancer. Studies are not conclusive. One line of reasoning suggests alcohol-based mouthwashes add to the effects of alcohol consumed by heavy drinkers. Alcohol-based mouthwashes can be avoided.

QUESTIONS TO ASK THE DOCTOR

- In which stage is the cancer?
- What is the outlook for a patient with my profile?
- What are the side effects of the treatments that are recommended? Which treatment gives the best combination of survival and quality of life?
- Is there a clinical trial for which I am eligible?

See also Cigarettes; Oral cancer; Nasopharyngeal cancer; Smoking cessation.

Resources

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American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS). 310 South Henry Street, Alexandria, VA 22314. (703) 299-9291. <www.facemd.org>.

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Osteosarcoma

Definition

Osteosarcoma, also called osteogenic **sarcoma**, is a type of cancer that develops from bone. Osteosarcoma is destructive at its original area and is likely to spread to other parts of the body.

Description

Osteosarcoma is a malignant (cancerous) tumor that arises from bone itself, and is thus called a primary bone cancer. Primary bone cancers are relatively rare overall. Approximately 2,400 new cases of osteosarcoma occur in the United States every year.

Osteosarcoma occurs most frequently during childhood or adolescence. About 60% of cases of this disease develop during the second decade of life. The incidence of osteosarcoma rises again among people in their 40s and 50s.

Osteosarcoma may occur in any bone, but develops most commonly in long bones, particularly near the knee or in the upper arm. The cancer starts growing within a bone and forms an expanding, ball-like mass. The tumor eventually breaks through the surface of the bone and begins to invade adjoining structures such as muscles. If untreated, the disease usually appears elsewhere in the same limb and metastasizes to distant parts of the body, such as the lungs.

Causes and symptoms

There are numerous theories regarding the causes of osteosarcoma. Many cases occur during a time of rapid bone growth, as in teenagers or people with Paget's disease. This suggests that the cancer may develop when the body loses its ability to control the multiplication of certain bone cells. Some cases of osteosarcoma are likely to have a genetic basis, and numerous genetic abnormalities have been found in patients with osteosarcoma. Osteosarcoma is also the most common second cancer to develop in survivors of **retinoblastoma**, a cancer of the eye that often has a genetic cause. Other cases arise in people who have been exposed to radiation, either accidentally or as part of a medical treatment.

The most common early symptoms of osteosarcoma are often vague. There may be pain or swelling at the site of the tumor, but these symptoms initially may not seem serious in a young, active person. Thus, the patient or medical personnel may attribute the symptoms to growing pains, or an injury from sports, for example, and the diagnosis may be delayed. Eventually, it is usually possible to feel a firm lump on the bone, and this lump will be uncomfortable to the touch.

Diagnosis

The complete diagnosis of osteosarcoma is a complicated process, requiring a variety of tests and the help of several types of medical specialists. Physicians must determine the stage of the cancer (the extent to which it has spread), and the grade of the cancer (the degree of cancerous qualities shown by its cells in a **biopsy** specimen). A higher grade or stage indicates a more serious disease than does a lower grade or stage.

Initial diagnosis begins with x-ray images of the affected area. These pictures will show a destructive growth within the bone, which is often described as having a "moth-eaten appearance". The patient then requires further imaging tests such as **computed tomography** (CT, CAT) or magnetic resonance (MR, MRI) scans of the tumor, a chest x-ray series or chest CT, and a nuclear medicine scan of the entire skeleton (bone scan). Blood tests, such as measurements of alkaline phosphatase (alk phos) provide additional information. These tests all help determine the stage of the cancer.

Finally, physicians require a biopsy sample of the diseased bone, obtained with a needle or by a surgical procedure, to be sure that the disease is truly cancer and to identify its grade. There are numerous tests, mostly involving examinations under the microscope, to perform on this biopsy specimen.

Treatment and prognosis

Before the 1980s, limb **amputation** was the standard treatment for osteosarcoma. Usually, however, the tumor had already spread elsewhere in the body and the patient eventually died of the disease. Overall results were dismal.

KEY TERMS

Alkaline phosphatase (Alk phos)—A body protein, measurable in the blood, that often appears in high amounts in patients with osteosarcoma. However, many other conditions also elevate the level of alkaline phosphatase.

Chemotherapy—A type of treatment for cancer that attempts to kill tumor cells with doses of powerful, often toxic, chemicals.

Grade—As a noun: a classification of the cancerous qualities of an individual tumor. A higher grade indicates a more serious disease than does a lower grade. As a verb: to classify the cancerous qualities of an individual tumor.

Malignant—Cancerous.

Metastasize—To spread to another part of the body.

Monoclonal antibody—A protein, produced in large quantities in a laboratory, designed to attack a specific target in the body.

Osteogenic—Creating bone.

Osteogenic sarcoma—Osteosarcoma.

Paget's disease—A non-cancerous disease marked by excessive growth of abnormal bone material.

Retinoblastoma—A cancerous tumor of the eye.

Stage—As a noun - the extent to which an individual cancer has spread. A higher stage indicates a more serious disease than does a lower stage. As a verb - to determine the extent to which an individual cancer has spread.

Tumor—An abnormal growth of cells in the body. Tumors may be benign (non-cancerous) or malignant.

Newer medical developments make it possible to avoid amputation and yet treat many patients with osteosarcoma successfully. Patients almost always receive **chemotherapy** with more than one drug (multi-drug therapy) before surgery to shrink the original cancer and reduce the likelihood of spread to other areas. Techniques known as limb-sparing surgery often allow removal of the tumor while saving the rest of the extremity. Afterward, patients usually continue to receive chemotherapy, and may require bone grafts or prosthetic devices to replace parts of bones or joints that have been removed.

Future treatments under investigation include **monoclonal antibodies** that destroy specific cancer cells, techniques to slow cancer growth by controlling certain cellular genes, and bone-seeking substances that directly target areas of active bone growth.

Alternative and complementary therapies

Current treatments with chemotherapy and surgery offer a substantial improvement over past therapies. Radiation treatment has not been effective. Complementary and alternative medicine techniques may improve a patient's sense of well-being but will not cure this destructive type of cancer.

Prognosis

Prognosis for an individual patient reflects a complex balance among the extent to which the cancer has already spread at the time of diagnosis, the aggressiveness of the cells within the cancer, and the response to chemotherapy. Early detection is extremely important. The best chance of cure occurs when a tumor shows no sign of **metastasis** at the time of original surgery, is well-confined within a single bone and is completely removed, and responds well to chemotherapy. The five-year survival rate for osteosarcoma in a long bone of a limb is about 70%. All patients must be followed closely by a physician to watch for cancer recurrence.

Prevention

Prevention of osteosarcoma is difficult since doctors do not know the cause of most cases. Perhaps research eventually will make prevention possible. Early detection of the disease remains vital. Anyone with persistent pain in a bone or limb should report this to a physician. People with special risk factors including Paget's disease, exposure to significant amounts of radiation, or a family history of certain types of cancer must be especially vigilant.

Resources

PERIODICALS

Marina, Neyssa, et al. "Biology and Therapeutic Advances for Pediatric Osteosarcoma." *The Oncologist* 9 (2004): 422-41.

Wittig, James C., et al. "Osteosarcoma: A Multidisciplinary Approach to Diagnosis and Treatment." *American Family Physician* 65 (2002): 1123-32, 1135-6.

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Ovarian cancer

Definition

Ovarian cancer is cancer of the ovaries, the egg-releasing and hormone-producing organs of the female reproductive tract. Cancerous, or malignant, cells divide and multiply in an abnormal fashion.

Description

The ovaries are small, almond-shaped organs, located in the pelvic region, one on either side of the uterus. When a woman is in her childbearing years, the ovaries alternate to produce and release an egg each month during the menstrual cycle. The released egg is picked up by the adjacent fallopian tube, and continues down towards the uterus. The ovaries also produce and secrete the female hormones estrogen and progesterone, which regulate the menstrual cycle and pregnancy, as well as support the development of the secondary female sexual characteristics (breasts, body shape, and body hair). During pregnancy and when women take certain medications, such as oral contraceptives, the ovaries are given a rest from their usual monthly duties.

Types of ovarian cancers

Ninety percent of all ovarian cancers develop in the cells lining the surface, or epithelium, of the ovaries and so are called epithelial cell tumors. About 15% of epithelial cancers are considered low malignant potential or LMP tumors. These tumors occur more often in younger women, and are more likely to be caught early, so prognosis is good.

Germ cell tumors develop in the egg-producing cells of the ovary, and comprise about five percent of ovarian tumors. These tumors are usually found in teenage girls or young women. The prognosis is good if found early, but as with other ovarian cancers, early detection is difficult.

Primary peritoneal **carcinoma** (PPC) is a cancer of the peritoneum, the lining of the abdominal cavity where the internal organs are located. Although it is a distinct disease, it is linked with ovarian cancer. This is because the ovarian and peritoneal cells have the same embryonic origin. This means that the very early cells of the embryo that will ultimately develop into the ovaries and the peritoneum share a common origin. The term *primary* means that the cancer started first in the peritoneum, as opposed to the cancer starting in the ovary and then moving, or metastasizing, into the peritoneum.

Demographics

Ovarian cancer can develop at any age, but is most likely to occur in women who are 50 years or older. More than half the cases are among women who are aged 65 years and older. Industrialized countries have the highest incidence of ovarian cancer. Caucasian women, especially of Ashkenazi Jewish descent, are at somewhat higher risk; African-American and Asian women are at a slightly lower risk. The risk of developing the disease increases with age. Ovarian cancer is the fourth most common cancer among women in the United States, and the second most common gynecologic cancer. It accounts for 4% of all cancers in women. However, because of poor early detection, the death rate for ovarian cancer is higher than for that of any other cancer among women. About 1 in 70 American women will develop ovarian cancer during her lifetime, and 1 in 100 will die from it. The American Cancer Society estimates about 26,000 new cases of ovarian cancer in 2004 in the United States, and about 16,000 deaths.

Only 50% of the women who are diagnosed with ovarian cancer will survive five years after initial diagnosis. This is due to the cancer being at an advanced stage at the time of diagnosis. With early detection, however, survival at five years post diagnosis may be 95%.

Causes and symptoms

Causes

The actual cause of ovarian cancer remains unknown, but several factors are known to increase one's chances of developing the disease. These are called risk factors. Women at a higher risk than average of developing ovarian cancer include women who:

- have never been pregnant or had children
- are Caucasian, especially of Northern European or Askenazi Jewish descent
- are over 50. Half of all diagnosed cases are in women over 65.
- have a family history of breast, ovarian, endometrial (uterine), prostate or colon cancer
- have had **breast cancer**
- have a first-degree relative (mother, daughter, sister) who has had ovarian cancer. (The risk is greater if two or more first-degree relatives had the disease. Having a grandmother, aunt or cousin with ovarian cancer also puts a woman at higher-than-average risk.)
- have the genetic mutation BRCA1 or BRCA2. (Not all women with these genetic breast cancer mutations will develop ovarian cancer. By age 70, a woman who has

the BRCA1 mutation carries about a 40–60% risk of developing ovarian cancer. Women with the genetic mutation BRCA2 have a 15% increased risk of developing ovarian cancer. However, heredity only plays a role in about 5–10% of cases of ovarian cancer.)Women who have a strong familial history may benefit from genetic counseling to better understand their risk factors.

In addition to the above risk factors, the following factors appear to play a role in affecting a women's chances of developing ovarian cancer.

REPRODUCTION AND HORMONES. Early menstruation (before age 12) and late menopause seem to put women at a higher risk for ovarian cancer. This appears to be because the longer, or more often, a woman ovulates, the higher her risk for ovarian cancer. As mentioned above, women who were never pregnant have a higher risk of developing the disease than women with one or more pregnancies. It is not yet clear from research studies whether a pregnancy that ends in miscarriage or stillbirth lowers the risk factor to the same degree as the number of term pregnancies. The use of post-menopausal estrogen supplementation for 10 years or more may double a woman's risk of ovarian cancer. Short-term use does not seem to alter one's risk factor.

INFERTILITY DRUG-STIMULATED OVULATION. Research studies have reported mixed findings on this issue. It appears that women who take medications to stimulate ovulation, yet do not become pregnant, are at higher risk of developing ovarian cancer. Women who do become pregnant after taking fertility drugs do not appear to be at higher risk. One study reported that the use of the fertility drug clomiphene citrate for more than a year increased the risk of developing LMP tumors. LMP tumors respond better to treatment than other ovarian tumors.

TALC. The use of talcum powder in the genital area has been implicated in ovarian cancer in many studies. It may be because talc contains particles of asbestos, a known carcinogen. Female workers exposed to asbestos had a higher-than-normal risk of developing ovarian cancer. Genital deodorant sprays may also present an increased risk. Not all studies have brought consistent results.

FAT. A high-fat diet has been reported in some studies to increase the risk of developing ovarian cancer. In one study the risk level increased with every 10 grams of saturated fat added to the diet. This may be because of its effect on estrogen production.

Symptoms

Most of the literature on ovarian cancer states that there are usually no early warning symptoms for the disease. Ovarian cancer is often referred to as a silent killer, because women either are unaware of having it, or have symptoms that are not accurately diagnosed until the disease is in an advanced state. However, a November 2000 study reported in the medical journal *Cancer* analyzed more than 1,700 questionnaires completed by women with stage III and stage IV ovarian cancer. The researchers found that 95% of the women reported having had early symptoms that they brought to their doctors. Most symptoms were somewhat vague and either abdominal or gastrointestinal in nature, and consequently were either not properly diagnosed or were recognized as being ovarian in nature only after a significant length of time had passed.

The following symptoms are warning signs of ovarian cancer, but could also be due to other causes. Symptoms that persist for two to three weeks, or symptoms that are unusual for the particular woman should be evaluated by a doctor right away.

- digestive symptoms, such as gas, indigestion, constipation, or a feeling of fullness after a light meal
- bloating, distention or cramping
- abdominal or low-back discomfort
- pelvic pressure or frequent urination
- unexplained changes in bowel habits
- nausea or vomiting
- pain or swelling in the abdomen
- loss of appetite (anorexia)
- **fatigue**
- unexplained weight gain or loss
- pain during intercourse
- vaginal bleeding in post-menopausal women

Diagnosis

In the best-case scenario a woman is diagnosed with ovarian cancer while it is still contained in just one ovary. Early detection can bring five-year survival to near 95%. Unfortunately, about 75% of women (3 out of 4) have advanced ovarian cancer at the time of diagnosis. (Advanced cancer is at stage III or stage IV when it has already spread to other organs.) Five-year survival for women with stage IV ovarian cancer may be less than 5%.

Diagnostic tests and techniques

If ovarian cancer is suspected, several of the following tests and examinations will be necessary to make a diagnosis.

- a complete medical history to assess all the risk factors
- a thorough bi-manual pelvic examination
- CA-125 assay
- one or more various imaging procedures
- a lower GI series, or **barium enema**
- diagnostic laparoscopy

BI-MANUAL PELVIC EXAMINATION The exam should include feeling the following organs for any abnormalities in shape or size: the ovaries, fallopian tubes, uterus, vagina, bladder, and rectum. Because the ovaries are located deep within the pelvic area, it is unlikely that a manual exam will pick up an abnormality while the cancer is still localized. However, a full examination provides the practitioner with a more complete picture. An enlarged ovary does not confirm cancer, as the ovary may be large because of a cyst or endometriosis. While women should have an annual **Pap test**, this test screens for **cervical cancer**. Cancerous ovarian cells, however, might be detected on the slide. Effectiveness of using Pap smears for ovarian cancer detection is about 10-30%.

CA-125 ASSAY This is a blood test to determine the level of CA-125, a biomarker or tumor marker. A tumor marker is a measurable protein-based substance given off by the tumor. A series of CA-125 tests may be done to see if the amount of the marker in the blood is staying stable, increasing or decreasing. A rising CA-125 level usually indicates cancer, while a stable or declining value is more characteristic of a cyst. The CA-125 level should never be used alone to diagnose ovarian cancer. It is elevated in about 80% of women with ovarian cancer, but in 20% of cases is not. In addition, it could be elevated because of a non-ovarian cancer, or it can be elevated with non-malignant gynecologic conditions, such as endometriosis or ectopic pregnancy. During menstruation the CA-125 level may be elevated, so the test is best done when the woman is not having her menstrual period.

IMAGING There are several different imaging techniques used in ovarian cancer evaluation. A fluid-filled structure such as a cyst creates a different image than does a solid structure, such as a tumor. An ultrasound uses high-frequency sound waves that create a visual pattern of echoes of the structures at which they are aimed. It is painless, and is the same technique used to check the developing fetus in the womb. Ultrasound may be done externally through the abdomen and lower pelvic area, or with a transvaginal probe.

Other painless imaging techniques are **computed tomography** (CT) and **magnetic resonance imaging** (MRI). Color Doppler analysis provides additional contrast and accuracy in distinguishing masses. It remains unclear whether Doppler is effective in reducing the high number of false-positives with transvaginal **ultrasonography**. These imaging techniques allow better visualization of the internal organs and can detect abnormalities without having to perform surgery.

LOWER GI SERIES A lower GI series, or barium enema, uses a series of x rays to highlight the colon and rectum. To provide contrast, the patient drinks a chalky liquid containing barium. This test might be done to see if the cancer had spread to these areas.

DIAGNOSTIC LAPAROSCOPY This technique uses a thin hollow lighted instrument inserted through a small incision in the skin near the belly button to visualize the organs inside of the abdominal cavity. If the ovary is believed to be malignant, the entire ovary is removed (**oophorectomy**) and its tissue sent for evaluation to the pathologist, even though only a small piece of the tissue is needed for evaluation. If cancer is present, great care must be taken not to cause the rupture of the malignant tumor, as this would cause spreading of the cancer to adjacent organs. If the cancer is completely contained in the ovary, its removal functions also as the treatment. If the cancer has spread or is suspected to have spread, then a saline solution may be instilled into the cavity and then drawn out again. This technique is called peritoneal lavage. The aspirated fluid will be evaluated for the presence of cancer cells. If peritoneal fluid is present, called **ascites**, a sample of this will also be drawn and examined for malignant cells. If cancer cells are present in the peritoneum, then treatment will be directed at the abdominal cavity as well.

RESEARCH AND NEW DIAGNOSTIC TESTS Many cancer researchers recognize the urgency of developing a new diagnostic test for ovarian cancer that is both sensitive and reliable. Some experts in the field look to proteomics, which is the large-scale identification and analysis of all the proteins in an organism or organ, to lead eventually to the development of a useful new test for ovarian cancer.

A group of researchers in Canada reported in 2003 that human kallikrein gene 14 (KLK14) might serve as a new biomarker for ovarian cancer. Kallikreins are a group of compounds that help to split up complex protein molecules into smaller units; prostate-specific antigen, or PSA, is a kallikrein. Early results of tests for KLK14 indicate that about 65% of women known to have ovarian cancer have elevated levels of this kallikrein.

Treatment team

A woman's treatment team may consist of her primary care physician, her gynecologist/surgeon, a

medical oncologist, a gynecologic oncologist, and a radiation oncologist. Professionals to address her psychological needs may also be part of the team, such as a medical social worker or a psychiatric nurse specializing in oncology. A case coordinator may also participate, as may individuals to address her spiritual and/or mind/body needs. The purpose of the team, versus seeing the various specialists independently, is to coordinate the care, treatments and appointments between the different team members. This allows all team members to know what everyone is doing, to coordinate appointments to minimize fatigue, and to make sure the physical, psychological, and spiritual needs of the patient are being addressed to the fullest degree possible.

Clinical staging, treatment, and prognosis

Clinical staging

Staging is the term used to determine if the cancer is localized or has spread, and if so, how far and to where. Staging helps define the cancer, and will determine the course of suggested treatment. Staging involves examining any tissue samples that have been taken from the ovary, nearby lymph nodes, as well as from any nearby organs or structures where **metastasis** was suspected. This may include the diaphragm, lungs, stomach, intestines and omentum (the tissue covering internal organs), and any fluid as described above.

The National Cancer Institute Stages for ovarian cancer are:

- Stage I: Cancer is confined to one or both ovaries.
- Stage II: Cancer is found in one or both ovaries and/or has spread to the uterus, fallopian tubes, and/or other body parts within the pelvic cavity.
- Stage III: Cancer is found in one or both ovaries and has spread to lymph nodes or other body parts within the cavity, such as the surfaces of the liver or intestines.
- Stage IV: Cancer is found in one or both ovaries and has spread to other organs such as the liver or lung.

The individual stages are also further broken down in detail, such as Ia, Ib, etc. Accurate staging is important for several reasons. Treatment plans are based on staging, in part because of trying to duplicate the best results achieved in prior research trials. When staging is inconsistent, it becomes more difficult to know how different research studies compare, so the results themselves cannot be relied upon.

Treatment

Treatment offered will primarily depend on the stage of the cancer and the woman's age. It is always appropriate to consider getting a second opinion, especially when treatment involves surgery, **chemotherapy**, and possible radiation. Before the patient makes her decision as to which course of treatment to take, she should feel that she has the information necessary with which to make an informed decision. The diagnostic tools mentioned above are used to determine the course of treatment. However, the treatment plan may need to be revised if the surgeon sees that the tumor has spread beyond the scope of what was seen during diagnostic tests.

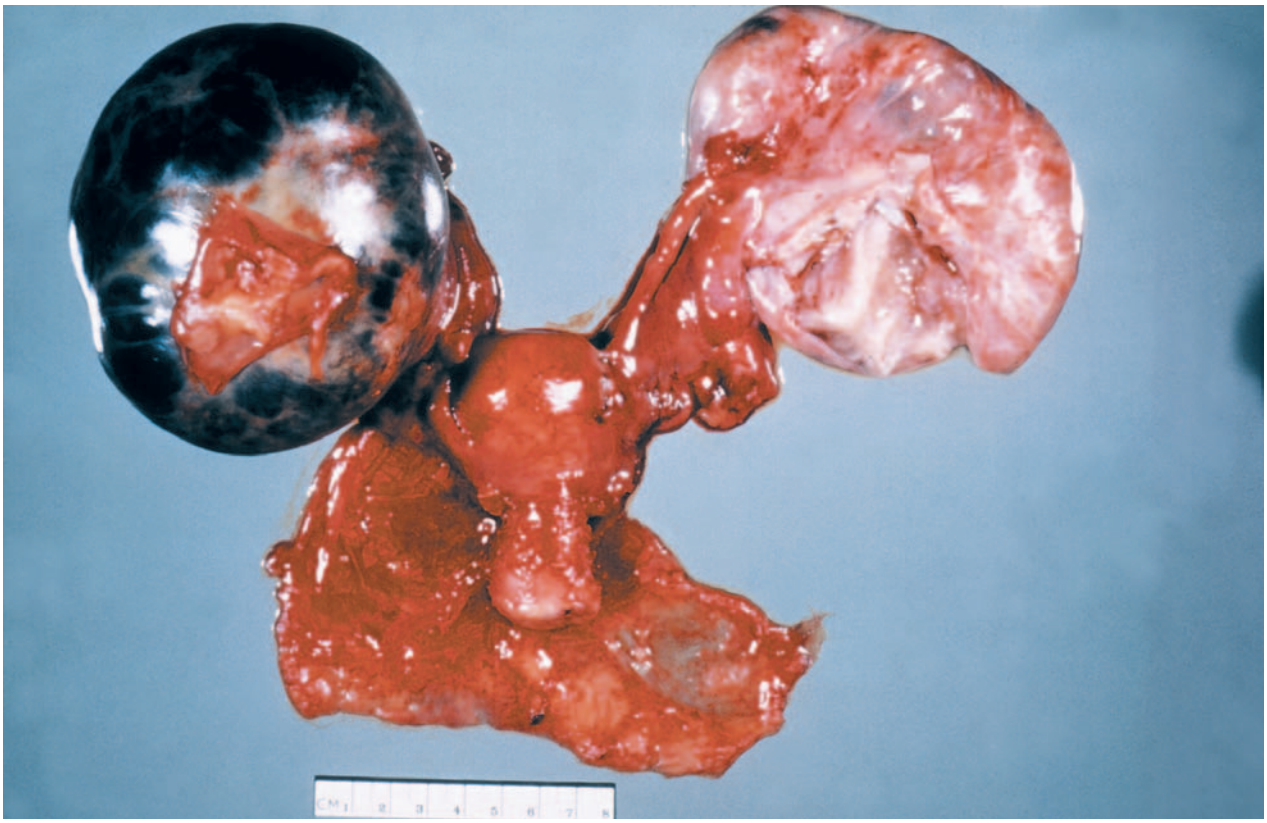
SURGERY Surgery is done to remove as much of the tumor as possible (called tissue debulking), utilizing chemotherapy and/or radiation to target cancer cells that have remained in the body, without jeopardizing the woman's health. This can be hard to balance once the cancer has spread. Removal of the ovary is called oophorectomy, and removal of both ovaries is called bilateral oophorectomy. Unless it is very clear that the cancer has not spread, the fallopian tubes are usually removed as well (salpingo-oophorectomy). Removal of the uterus is called hysterectomy.

If the woman is very young, all attempts will be made to spare the uterus. It is crucial that a woman discuss with her surgeon her childbearing plans prior to surgery. Unfortunately, ovarian cancer spreads easily and often swiftly throughout the reproductive tract. It may be necessary to remove all reproductive organs as well as part of the lining of the peritoneum to provide the woman with the best possible chance of long-term survival. Fertility-sparing surgery can be successful if the ovarian cancer is caught very early.

Side effects of the surgery will depend on the extent of the surgery, but may include pain and temporary difficulty with bladder and bowel function, as well as reaction to the loss of hormones produced by the organs removed. A hormone replacement patch may be applied to the woman's skin in the recovery room to help with the transition. An emotional side effect may be the feeling of loss stemming from the removal of reproductive organs.

Chemotherapy

Chemotherapy is used to target cells that have traveled to other organs, and throughout the body via the lymphatic system or the blood stream. Chemotherapy drugs are designed to kill cancer cells, but may also be harmful to healthy cells as well. Chemotherapy may be administered through a vein in the arm (intravenous, IV), may be taken in tablet form, and/or may be given through a thin tube called a catheter directly into the abdominal cavity (intraperitoneal). IV and oral chemotherapy drugs travel throughout the body; intraperitoneal chemotherapy is localized in the abdominal cavity.



Excised female reproductive organs, showing a cancerous ovary (left, black). *(©St. Bartholomew's Hospital, Science Source/ Photo Researchers, Inc. Reproduced by permission.)*

Side effects of chemotherapy can vary greatly depending on the drugs used. Currently, chemotherapy drugs are often used in combinations to treat advanced ovarian cancer, and usually the combination includes a platinum-based drug (such as **cisplatin**) with a taxol agent, such as **paclitaxel**. Some of the combinations used or being studied include: carboplatin/paclitaxel, cisplatin/paclitaxel, cisplatin/topotecan, and cisplatin/carboplatin. As new drugs are evaluated and developed, the goal is always for maximum effectiveness with minimum of side effects. Side effects include **nausea and vomiting**, **diarrhea**, decreased appetite and resulting **weight loss**, fatigue, headaches, loss of hair, and numbness and tingling in the hands or feet. Managing these side effects is an important part of cancer treatment.

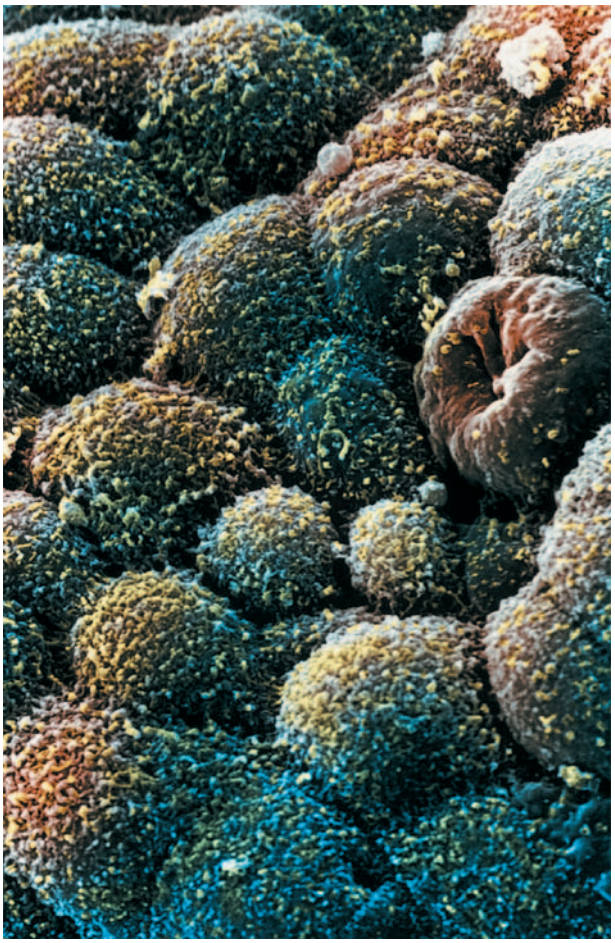
After the full course of chemotherapy has been given, the surgeon may perform a "second look" surgery to examine the abdominal cavity again to evaluate the success of treatment.

RADIATION Radiation uses high-energy, highly focused x rays to target very specific areas of cancer. This is done using a machine that generates an external beam. Very careful measurements are taken so that the targeted area can be as focused and small as possible. Another form of radiation uses a radioactive liquid that is administered into the abdominal cavity in the same fashion as intraperitoneal chemotherapy. Radiation is usually given on a daily Monday though Friday schedule and for several weeks continuously. Radiation is not painful, but side effects can include skin damage at the area exposed to the external beam, and extreme fatigue. The fatigue may hit suddenly in the third week or so of treatment, and may take a while to recover even after treatments have terminated. Other side effects may include nausea, vomiting, diarrhea, loss of appetite, weight loss and urinary difficulties. For patients with incurable ovarian cancer, radiation may be used to shrink tumor masses to provide pain relief and improve quality of life.

Once the full course of treatment has been undertaken, it is important to have regular follow-up care to monitor for any long-term side effects as well as for future relapse or metastases.

Alternative and complementary therapies

The term alternative therapy refers to therapy utilized instead of conventional treatment. By definition,



Colored scanning electron micrograph (SEM) of cancer cells in the ovary. These tumor cells are a variety of shapes and sizes, typical of the chaotic arrangement and growth of malignant cancer cells. *(Copyright Quest, Science Source/ Photo Researchers, Inc. Photo reproduced by permission.)*

these treatments have not been scientifically proven or investigated as thoroughly and by the same standards as conventional treatments. The terms complementary or integrative therapies denote practices used in conjunction with conventional treatment. Regardless of the therapies chosen, it is key for patients to inform their doctors of any alternative or complementary therapies being used or considered. (Some alternative and complementary therapies adversely affect the effectiveness of conventional treatments.) Some common complementary and alternative medicine techniques and therapies include:

- prayer and faith healing
- meditation
- mind/body techniques such as support groups, visualization, guided imagery and hypnosis
- energy work such as Therapeutic Touch and Reiki
- acupuncture and Chinese herbal medicine
- body work such as yoga, massage and t'ai chi
- vitamins and herbal supplements
- diets such as vegetarianism and macrobiotic

Mind/body techniques along with meditation, prayer, yoga, t'ai chi, and acupuncture have been shown to reduce stress levels, and the relaxation provided may help boost the body's immune system. The effectiveness of other complementary and alternative treatments is being studied by the National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM). For a current list of the research studies occurring, results of recent studies, or publications available, patients can visit the NCCAM web site or call at (888) 644-6226.

Prognosis

Prognosis for ovarian cancer depends largely on the stage at which it is first diagnosed. While stage I cancer may have a 95% success rate, stages III and IV may have a survival rate of 17-30% at five years post-diagnosis. Early detection remains an elusive, yet hopeful, goal of research. Also, **clinical trials** are addressing new drug and treatment combinations to prolong survival in women with more advanced disease. Learning one's family history may assist in early detection, and genetic studies may clarify who is at greater risk for the disease.

Coping with cancer treatment

While the cancer may only be in part of the body, it is very much a full mind/body experience. Strategies for coping with the treatment need to address the entire range of the experience. Each woman will have different needs. She might want to create a personal support team of friends. They can provide support by:

- Finding helpful information in the library or on the Internet about clinical trials, new therapies or treatments, different treatment centers, etc.
- Providing transportation to and from appointments. A diagnosis of cancer can be overwhelming. In such a stressful and distracted state it is often hard to remember what a doctor has said, or even to remember the questions to be asked. Having a second set of ears during this stressful time can be helpful.
- Helping with household duties so that the woman can rest after treatments and have more energy to devote to her family.
- Assisting with child care. Children are very much affected by a parent's cancer diagnosis, whether they

KEY TERMS

Biomarker—A biochemical substance that can be detected in blood samples and indicates the presence of a cancerous tumor.

Gynecologic oncologist—A physician specializing in the treatment of cancers of the female reproductive tract.

Kallikrein—Any of a group of compounds in the body known as serine endopeptidases that help to break down proteins into smaller units. Prostate-specific antigen belongs to this group of chemicals. A recently discovered kallikrein may be useful as a biomarker for ovarian cancer.

Lymphatic system—A connected network of nodes, or glands that carry lymph throughout the body. Lymph is a fluid that contains the infection-fighting white blood cells that form part of the body's immune system. Because the network goes throughout the body, cancer cells that enter the lymphatic system can travel to and be deposited at any point into the tissues and organs and form new tumors there.

Pathologist—The pathologist is a doctor specializing in determining the presence and type of disease by looking at cells and tissue samples.

QUESTIONS TO ASK THE DOCTOR

- What tests will be used to look for and diagnose my cancer?
- How should I prepare for the tests?
- What will take place during the test? Will it be painful? What can I do to decrease the pain?
- When will I learn the results?
- Once the results are in: What do these results mean?
- What type and stage is my cancer?
- What are my treatment options?
- Who will be involved in my care?
- What clinical trials would benefit me?
- What changes in my ability to work or perform my daily functions should I expect during treatment?
- How long will my treatment last?
- What side effects should I expect from treatment?
- Are there any conventional or alternative therapies that can diminish these side effects?
- How soon after treatment will I be able to resume my regular activities?
- What is the plan for my follow-up care?

have been fully informed or not of what is taking place. For a child to go to a friend's house can provide a sense of normalcy and security.

- Being available to participate in activities and conversations not centering on the cancer. While in the midst of cancer treatments, it is important to talk about non-cancer issues as well, and to maintain social relationships and activities. It is important for the cancer patient to keep at least some of the social outlets she had before the diagnosis.

A woman may wish to join a support group of women with ovarian cancer. This group can provide the environment to talk about the diagnosis, the treatments, the side effects and the impact the diagnosis has on her life with others who can empathize. If there is no support group nearby, she may be able to start one, or use one on the Internet. Studies examining support groups for children of a parent with cancer have shown these groups to be helpful for the child as well.

Clinical trials

Clinical trials are human research studies. Their goal is to evaluate the effectiveness of new ways to treat cancer. There are many different designs, and they target different aspects of care. For example, some may investigate the response of different chemotherapy drugs, while another study may compare different types of treatment/chemotherapy combinations. The Cancer Information Service (CIS) is a division of the National Cancer Institute, the United States government agency for cancer research. Their web site contains information on all ongoing research trials, the areas being researched, and whether or not individuals can still participate.

Research studies are usually designed to compare a new treatment method against the standard method, or the effectiveness of a drug against a placebo (an inert substance that would be expected to have no effect on the outcome). Since the research is experimental in nature, there are no guarantees about the outcome. New drugs being used may have harmful, unknown side effects. Some people participate to help further knowledge about their disease. For others, the study may provide a possible treatment that is not yet available

otherwise. If one participates in a study and is in the group receiving the standard care or the placebo, and the treatment group gets clear benefit, it may be possible to receive the experimental treatment once one's original participation role is over. Participants will have to meet certain criteria before being admitted into the study. It is important to fully understand one's role in the study, and weigh the potential risks versus benefits when deciding whether or not to participate.

As of late 2004, the National Cancer Institute (NCI) had nearly 150 clinical trials related to ovarian cancer in its database. Most of these trials are devoted to combination chemotherapy or chemotherapy administered after surgery, but they also include studies of stem cell transplantation, newer drugs like amifostine, pain management and supportive care for advanced ovarian cancer, and cancer vaccines.

Prevention

Since the cause of ovarian cancer is not known, it is not possible to fully prevent the disease. However, there are ways to reduce one's risks of developing the disease.

DECREASE OVULATION. Pregnancy gives a break from ovulation, and multiple pregnancies appear to further reduce the risk of ovarian cancer. The research is not clear as to whether the pregnancy must result in a term delivery to have full benefit. Women who breastfeed their children also have a lower risk of developing the disease. Since oral contraceptives suppress ovulation, women who take birth control pills (BCPs), even for as little as 3 to 6 months have a lower incidence of the disease. It appears that the longer a woman takes BCPs, the lower her risk for ovarian cancer. Also, this benefit may last for up to 15 years after a woman has stopped taking them. However, since BCPs alter a woman's hormonal status, her risk for other hormonally related cancers may change. For this reason it is very important to discuss all the risks and benefits with one's health care provider.

GENETIC TESTING. **Genetic testing** is available which can help to determine whether a woman who has a family history of breast, endometrial, or ovarian cancer has inherited the mutated BRCA gene that predisposes her to these cancers. If the woman tests positive for the mutation, then she may be able to choose to have her ovaries removed. Even without testing for the mutated gene, some women with strong family histories of ovarian cancer may consider having their ovaries removed as a preventative measure (prophylactic oophorectomy). This procedure diminishes but does not completely remove the risk of cancer, as some women may still develop primary peritoneal carcinoma after oophorectomy.

SURGERY. Procedures such as tubal ligation (in which the fallopian tubes are blocked or cut off) and hysterectomy (in which the uterus is removed) appear to reduce the risk of ovarian cancer. However, any removal of the reproductive tract organs has surgical as well as hormonal side effects.

SCREENING. There are no definitive tests or screening procedures as of early 2005 to detect ovarian cancer in its early stages. Women at high risk should consult with their physicians about regular screenings, which may include transvaginal ultrasound and the blood test for the CA-125 protein.

The American Cancer Society recommends annual pelvic examinations for all women after age 40, in order to increase the chances of early detection of ovarian cancer.

Special concerns

Early detection remains the key focal point because the more ovarian cancer has spread, the poorer the chance for survival past a few years. As women and practitioners become more aware of the vague early warning signs, and seek out more accurate family histories, earlier screening can begin to lead to earlier detection and improved treatment success.

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National Cancer Institute. Building 31, Room 10A31, 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (301) 435-3848. <http://www.nci.nih.gov>.

National Center for Complementary and Alternative Medicine. NCCAM Clearinghouse, P.O. Box 8218, Silver Spring, MD 20907-8218. (888) 644-6226. <http://nccam.nih.gov>.

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Rebecca J. Frey, Ph.D.

Ovarian cystadenocarcinoma, Primary peritoneal carcinoma *see* **Ovarian cancer**

Ovarian epithelial cancer

Definition

Ovarian epithelial cancer is a type of cancer that develops in the cells that line the surface of the ovaries.

Description

Part of the female reproductive system, the ovaries are a pair of almond-shaped organs that are located on either side of the uterus, just above the pelvic bone. The ovaries produce estrogen and progesterone, which are female hormones. At birth, each ovary contains thousands of eggs. During a woman's fertile years, one ripened egg (or sometimes more) is released each month into a fallopian tube. As the egg takes its journey toward the uterus, a sperm can fertilize it. When a baby is conceived, it stays in the uterus until birth. During the birth process, powerful muscles in the uterus help to push the baby out through the cervix and vagina.

When an ovarian cell becomes cancerous, it tends to multiply quickly, forming a growth (or tumor). The resulting tumor may interfere with the way the ovary normally functions, but not in every case. Sometimes the cancer cells break off from the tumor and spread contiguously, which means they spread to nearby organs, such as to other areas of the pelvis.

Demographics

Although **ovarian cancer** rates differ significantly from country to country, Europe has been recognized as having one of the highest incidence rates of ovarian cancer in the world. Having carefully studied the ovarian cancer trends of twenty-eight European countries, Bray and colleagues reported in a 2004 article published by the *International Journal of Cancer* that European countries with the highest ovarian cancer rates in the past included the Nordic countries, Austria, Germany, and the United Kingdom, but current trends in these and other northern European countries showed a decline in ovarian cancer rates, especially with regard to mortality. However, the opposite was found to be true with regard to some of the southern and eastern European countries. In the Czech Republic and Hungry, there has been a drop in the mortality rates associated with ovarian cancer, but not a drop in the number of cases diagnosed. Bray a colleagues reported that "recent trends in ovarian cancer have led to a leveling of rates across various areas of the [European] continent, although a 2.5-fold variation was still observed in the late 1990s between the highest mortality rate of 9.3/100,000 in Denmark and the lowest one of 3.6 in Portugal."

The American Cancer Society estimates that 22,220 news cases of ovarian cancer will be diagnosed in the United States in 2005, resulting in approximately 16,210 deaths. Rarely seen in women under the age of 30, the risk of developing ovarian cancer increases with age. Nearly 90% of all the cases of ovarian cancer are ovarian epithelial cancer. Ranked fifth as the most

frequent cause of cancer death in women, ovarian epithelial cancer most commonly occurs in women over the age of 65.

Causes and symptoms

The presence of mutations in the BRCA1 and BRCA2 genes increase a woman's risk of developing breast or ovarian cancer, including ovarian epithelial cancer. When these gene mutations are not present in woman who has ovarian epithelial cancer, it is difficult to identify the cause. Several factors may increase a woman's risk of developing ovarian epithelial cancer, such as having a close relative with the disease or a personal history of **breast cancer**.

There seems to be a connection between the development of ovarian epithelial cancer and the number of times a woman ovulates in her lifetime. Statistics show that a woman who ovulates less seems to have less risk. For example, a woman who has had a child may have a decreased risk of developing ovarian epithelial cancer, because she has had a nine-month break in ovulation. On the other hand, a woman who has used birth control pills may lessen her risk for the same reason, because she, too, has had a break in ovulation.

Ovarian epithelial cancer often produces no symptoms in its early stages; therefore, by the time it is discovered, the disease is often widespread. In addition, women often ignore the symptoms, because they don't identify them with anything serious. Some of the symptoms include:

- gas and indigestion
- bloating
- swelling of the abdomen
- constipation, nausea, and vomiting
- fullness or pressure in the pelvis
- abnormal bleeding from the vagina
- lower abdominal pain (such as cramps)

Diagnosis

A variety of tests and examinations are used to diagnose ovarian epithelial cancer.

Pelvic Exam

Many women are familiar with this exam and schedule one on a yearly basis along with a pap smear. The exam is usually performed by a gynecologist, but is also sometimes performed by a physician specializing in family or internal medicine. Many women think a Pap smear will detect ovarian cancer, but, in truth, it is the pelvic examination that helps a physician diagnose ovarian epithelial cancer, whereas the Pap smear is useful in detecting **cervical cancer**.

To perform a pelvic examination, the physician inserts one or two lubricated, gloved fingers of one hand into a woman's vagina while pressing down on her abdomen with the other hand. By touch, the physician examines the uterus and ovaries, checking for any abnormalities in shape, size, or position. This examination only takes a few minutes and is not painful, although some women may feel some pressure or minor discomfort. The patient should tell the physician immediately if any pain is experienced. As part of the examination, the physician will also insert a lubricated, gloved finger into the rectum to feel for lumps.

Ultrasound

Often referred to as a sonogram, ultrasound is a completely painless procedure performed by radiologist in which high-energy sound waves are bounced off internal organs.

Magnetic Resonance Imaging (MRI)

Although an expense test, an MRI is often covered by many insurance plans. Using a magnetic field and imaging waves, an MRI scans a specific portion of the body from any angle. Painless and noninvasive, MRI testing does not require the use of contrast dye. However, the MRI is an unnerving machine for anyone claustrophobic, because the machine surrounds almost the entire body. Claustrophobic patients should ask their physician to refer them to the nearest Open Air MRI facility. The open design of an Open Air MRI provides access from all four sides and allows patients to feel more comfortable during their exam.

Blood Test

A test that measures the level of CA 125 in the blood is often recommended if ovarian epithelial cancer is suspected. An increased level of CA 125 may be a sign that cancer is present in the body.

Barium Enema

Sometimes referred to as a lower GI, a liquid that contains barium is put into the rectum, which coats the gastrointestinal tract so that x rays can be taken. It is usually performed by an x-ray technician or radiologist and is considered by many people to be as unpleasant as a normal enema.

Intravenous Pyelogram (IVP)

The purpose of this test, which normally takes about thirty minutes to an hour, is to see if any abnormalities exist in the kidneys and bladder. An IVP is essentially a series of x rays. A contrast dye, which is injected into the patient's vein, enhances the x-ray images that are taken to see if there are any blockages.

The night before the exam, the patient will be asked to fast (not eat any food) and to take a mild laxative, such as a teaspoon of castor oil. Patients who suspect they might be pregnant should inform their physicians prior to having an IVP. Although it is often not necessary for patients to remove their clothing, they will often be asked to remove any jewelry that might interfere with the images.

An IVP itself is painless, although some patients experience nausea and/or a metallic taste in their mouth as the dye is being inserted. Both the nausea and metallic taste tend to go away as the patient's body gets used to the dye. Some patients develop hives, which is an allergic reaction to the dye. The radiologist, who performs the test, will have medication on hand to treat the hives. When the test is completed, the radiologist will examine the x rays and write up a report for the referring physician who will deliver the results to the patient.

Computerized Tomography (CT Scan)

A CT scan, also referred to as a CAT scan, is a procedure that takes a series of detailed pictures of the inside of the body and is considered one of the best tools available for studying abdominal tissue, especially with regard to the presence of a tumor.

Like an IVP, a contrast dye is injected into a vein to help the organs and surrounding tissue show up more clearly. In some cases, the contrast dye is swallowed by the patient rather than injected. A computer linked to an x-ray machine generates the pictures. The test is painless and generally takes about thirty minutes to an hour, depending on how many images are needed. Unlike the IVP, however, the x-ray technician or radiologist will not remain in the room while the x rays are being taken. The patient will be able to hear and speak to the person performing the test, which is either an x-ray technician or radiologist. Because of the radiation used to perform a CT scan, patients that suspect they are pregnant should tell their physician prior to having the test. If the images show a tumor, many different specialists, such as a radiologist, oncologist, surgeon, and the referring physician, will often work together to arrive at a suitable course of treatment.

Biopsy

A physician may recommend that a **biopsy** be performed, which is a surgical procedure to remove tissue or cells from the surface of the ovary to see if they are cancerous.

Treatment team

The treatment team is comprised of physicians from a variety of medical specialties. For example, a patient diagnosed with ovarian epithelial cancer may have a treatment team that includes the patient's primary care physician and her gynecologist, as well as a radiologist, oncologist, surgeon, and **pain management** specialist. At-home caretakers are also part of the treatment team, providing important physical and emotional support to the patient. Physicians and patients that value a holistic approach to fighting cancer may add a variety of other advisors to the treatment team, such as psychologists, pastors, and alternative medicine specialists.

Clinical staging, treatments, and prognosis

Staging

After ovarian epithelial cancer has been diagnosed, it is classified as being in one of four stages based on whether the cancer cells have or have not spread within the ovaries or to other parts of the body. To determine the stage of the disease, the patient is placed under general anesthesia and a surgical procedure called a laparotomy is performed. By making an incision through the abdomen, the surgeon can inspect the ovaries and adjacent organs for cancer. A biopsy is often done at that time and the cells are viewed under a microscope by the surgeon who often specializes in oncology. If there are clear indications that cancerous tissue is present, the surgeon will usually remove it and any effected organs during the laparotomy. A tissue sample is also sent to a lab where a pathologist can further classify the sample and confirm the diagnosis. It can take several days to receive the pathologist's report.

The National Cancer Institute explains the four main stages of ovarian epithelial cancer as follows:

- Stage I: The cancer is present in one or both ovaries, but the cancer has not spread.
- Stage II: The cancer is present in one or both ovaries and has spread to the pelvis.
- Stage III: The cancer is present in one or both ovaries and has spread to other parts of the abdomen.
- Stage IV: The cancer is not only in one or both ovaries, but it has spread beyond the abdomen to other parts of the body.

KEY TERMS

Pap Smear—A procedure that involves taking cells from the cervix, which are examined under a microscope for signs of abnormality.

Peritoneum—The tissue that lines the abdomen.

QUESTIONS TO ASK YOUR DOCTOR

- What clinical trials do you recommend?
- Will I be able to have children?
- When will I be able to return to work?
- Are there any local cancer support groups?
- How will the treatment affect my sex life?
- Are there any medications that could alter the test or treatment results?
- What prescription and over-the-counter medications should be avoided during treatment?

All four stages have subcategories A, B, and C, which further indicate the characteristics and severity of the cancer within each stage. For example, according to the National Cancer Institute, in Stage IIIB, "The cancer has spread to the peritoneum but is 2 centimeters or smaller in diameter, whereas in Stage IIIC, the cancer has spread to the peritoneum and is larger than 2 centimeters and/or has spread to lymph nodes in the abdomen."

Treatment Options

Depending on the patient and the stage of the cancer, there are a variety of treatment options for patients with ovarian epithelial cancer. The three convention treatment options are surgery, **radiation therapy**, and **chemotherapy**. As the National Cancer Institute states, "Most patients have surgery to remove as much of the tumor as possible." Although ovarian epithelial cancer usually does not strike young women, it does pose a special concern for young women hoping to have a family. In the event that the disease is caught early enough, it might be possible to perform a unilateral salpingo-oophorectomy, which is the removal of only the involved ovary and fallopian tube, thereby giving the woman a chance to have children someday. However, in many cases, it is necessary to remove both ovaries, as well as the uterus, fallopian tubes, and nearby lymph glands. Sometimes it is even necessary to remove the omentum, which is a fold of the peritoneum.

Depending on the stage of cancer, radiation therapy may be recommended. There are generally two types of radiation therapy external radiation therapy, which comes from a machine outside of the body, and internal radiation therapy, such as implant radiation or brachytherapy. Chemotherapy is a commonly known cancer treatment that utilizes strong drugs to stop the growth of cancer cells. Chemotherapy is either given intravenously or orally; it often involves combination drug therapy. The administration and combination of chemotherapy drugs utilized is largely dependant on the extent of the cancer and the patient's medical profile.

Prognosis

The survival rate depends on a variety of factors, such as the patient's age and general health as well as the type and stage of tumor. When ovarian epithelial cancer is found early, the five-year survival rate is approximately 60% to 80%. However, because ovarian epithelial cancer is often found late in its development, the overall survival rate is 30% to 40%. In addition, ovarian epithelial cancer can recur after it has been treated.

Coping with cancer treatment

Patients having difficulty coping with the pain associated with cancer and chemotherapy might find it helpful to be referred to a physician who specializes in pain management or a pain clinic. Physicians specializing in the treatment of pain come from a variety of medical backgrounds, such as anesthesiology, obstetrics and gynecology, neurology, and surgery. Because of the complicated nature of cancer and cancer-related pain, ideally a pain management team should be formed that works with the patient's primary care physician, oncologist, and radiologist to provide comprehensive care to the patient.

Much has been written about coping with the physical side effects of cancer treatment; however, patients with ovarian epithelial cancer also face emotional challenges associated with their treatment. For example, women who are still in their reproductive years and need to have both ovaries removed must deal with an abrupt end to their reproductive choices. Women of all ages will have to deal with a variety of psychological issues, such as body image versus self-image. Some woman may need to be reminded, especially by family members and friends, that they are more than a collection of body parts. The spirit of their womanhood remains even if their ovaries do not.

It is important for cancer patients to understand that they are not alone. Support groups exist to help patients

cope not only with the physical aspects of having cancer, but with the psychological ones as well. Patients should be encouraged to talk about their feelings. The positive support (both emotional and otherwise) provided by caregivers can help to improve a patient's quality of life. In addition, support groups on the Internet have made it possible for women, even those in rural or remote areas, to reach out to one another in ways that allow anonymity.

Clinical trials

Patients should ask their doctor if there are any **clinical trials** being conducted in their areas that they should consider joining. Clinical trials are conducted to improve current methods of treatment or to develop new treatments. Patients with cancer who participate in clinical trials may improve their chances of survival.

Prevention

Women with a strong family history of ovarian epithelial cancer should be sure to have regular pelvic examinations, because an early diagnosis increases the chance of survival. However, there really is no way to prevent ovarian epithelial cancer, other than to have both ovaries removed before cancer has had a chance to grow, which is an extremely controversial prevention method. Nonetheless, some women with a high risk of developing ovarian epithelial cancer who have had the chance to have a family have elected to have a prophylactic **oophorectomy**, which is the medical name for the procedure that refers to the removal of healthy ovaries. Women considering this procedure need to know that it isn't necessarily a guarantee against ovarian cancer.

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Lee Ann Paradise

Oxaliplatin

Definition

Oxaliplatin is an investigational **chemotherapy** medicine used to treat certain types of cancer by destroying cancerous cells. Oxaliplatin is also known in other countries by its brand names Eloxatin and Transplatine. Other names for oxaliplatin include Oxalatoplatin, Oxalatoplatinum, 1-OHP or L-OHP, PR-54780.

Purpose

Oxaliplatin is not yet approved by the Food and Drug Administration in the United States. It is commercially available in Europe. Oxaliplatin has been used to treat metastatic colorectal cancer, and advanced **ovarian cancer** and has been tested with some results in head and neck cancers, skin cancer, lung cancer, and **non-Hodgkin's lymphomas**.

Description

Oxaliplatin is an analog of **cisplatin**, the first successful platinum-containing anticancer drug. It is one of the so-called DACH (1,2-Diamincyclohexane)-containing platinum complexes that exhibited activity in Murine L1210 leukemia tumor models possessing acquired resistance to cisplatin. These platinum-containing drugs interfere with the genetic material, or DNA, inside the cancer cells and prevent them from further dividing and growing more cancer cells.

Oxaliplatin has been used to treat cancer in **clinical trials** in the United States. It can be used alone to treat cancer or in combination with other chemotherapy medicines. Some of the other chemotherapy medicines that Oxaliplatin is commonly combined with include the drugs **fluorouracil** and calcium **leucovorin** and used in combination with cisplatin.

Recommended dosage

An oxaliplatin dose can be determined using a mathematical calculation that measures a person's body surface area (BSA). This number is dependent upon a patient's height and weight. The larger the person the greater the body surface area. Body surface area is measured in the units known as square meter (m^2). The body surface area is calculated and then multiplied by the drug dosage in milligrams per square meter (mg/m^2). This calculates the actual dose a patient is to receive.

Oxaliplatin is a clear colorless solution administered by an infusion into a vein. The infusion time period can vary. It can be given as a one-time dose every three weeks infused over 20 minutes up to six hours. There are multiple doses of oxaliplatin used in clinical trials dependent upon the type of cancer being treated. The doses have ranged from 20 mg per square meter daily for several days to 130 mg per square meter for one day every three weeks. Listed below are example dose recommendations for colorectal cancer and ovarian cancer.

To treat metastatic colorectal cancer

Oxaliplatin alone has been given at 130 mg per square meter administered into a vein for one day every three weeks. This did not have very good response rates.

Oxaliplatin is also given at a dose of 130 mg per square meter administered into a vein as a two- to six-hour infusion for one day every three weeks in combination with the chemotherapy drug fluorouracil.

To treat advanced ovarian cancer

Oxaliplatin alone has been given at 59 mg to 130 mg per square meter administered into a vein for one day as a 20-minute or two-hour infusion every three weeks.

Combination treatment of oxaliplatin at a dose of 130mg per square meter administered into a vein as a two-hour infusion every three weeks. The oxaliplatin must immediately follow a two hour-infusion of the chemotherapy drug cisplatin at a dose of 100 mg square meter every three weeks.

KEY TERMS

Anemia—A red blood cell count that is lower than normal.

Chemotherapy—Specific drugs used to treat cancer.

DNA—Genetic material inside of cells that allows for cells to function, separate into two cells and make more cells.

Food and Drug Administration—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives the approval to pharmaceutical companies for commercial marketing of their products.

Intravenous—To enter the body through a vein.

Metastatic—Cancer that has spread to one or more parts of the body.

Neutropenia—A white blood cell count that is lower than normal.

Precautions

When receiving the drug oxaliplatin it is important to avoid cold food and drinks.

Blood counts will be monitored regularly while on oxaliplatin therapy. During a certain time period after receiving oxaliplatin there is an increased risk of getting infections. Caution should be taken to avoid unnecessary exposure to germs.

Patients with a known previous allergic reaction to chemotherapy drugs should tell their doctors.

Patients who may be pregnant or trying to become pregnant should tell their doctors before receiving oxaliplatin.

Chemotherapy can cause men and women to be sterile or not able to have children.

Patients with existing or previous tingling or numbness in their hands and feet should tell their doctor before receiving oxaliplatin.

Patients should check with their doctors before receiving live virus **vaccines** while on chemotherapy.

Side effects

One of the most common side effects from receiving oxaliplatin is **nausea and vomiting**. Patients will be given medicines known as **antiemetics** before receiving

oxaliplatin to help prevent or decrease this side effect. **Diarrhea** and mouth sores have also been known to occur. The chance of these increase if the oxaliplatin is given along with the chemotherapy drug fluorouracil.

Oxaliplatin can commonly cause damage to nerves and nervous system tissues. Patients may feel tingling, numbness, and sometimes burning of the fingers and toes. This side effect is common, can be severe, and gets worse in the cold. The patient must inform the doctor if any of these symptoms are present. In addition, the patient may experience a tightness or spasm in their throat. The chance that this will happen increases if the patient is exposed to cold food or drinks while receiving oxaliplatin.

Low blood counts, referred to as **myelosuppression**, are expected due to oxaliplatin. The extent to which the blood counts fall due to oxaliplatin has been minimal. When the white blood cell count is low, this is called **neutropenia** and patients are at an increased risk of developing a **fever** and infections. There is a drug called Neupogen (filgrastim) that can be used to increase the white blood cell count.

Platelets are blood cells in the body that allow for the formation of clots. When the platelet count is low, patients are at an increased risk for bruising and bleeding. If the platelet count remains too low a platelet blood transfusion is an option. Low red blood cell counts, referred to as **anemia**, may also occur due to cisplatin administration. Low red counts make people feel tired and lacking energy. There is a drug called **erythropoietin** that can be used to increase the red blood cell count.

Oxaliplatin has caused severe allergic reactions known as anaphylaxis. The symptoms include difficulty breathing, drop in blood pressure, sweating, redness of the face, dizziness, headache, and a fast heart beat. This appears to be more common after several treatments with the drug oxaliplatin.

Less common side effects include hair loss (alopecia), fever, rash on hands and feet when given with fluorouracil, and fatigue. Oxaliplatin rarely causes kidney damage or hearing damage, unlike cisplatin chemotherapy.

All side effects a patient experiences should be reported to his or her doctor.

Interactions

Patients should avoid cold food and drinks while receiving oxaliplatin.

Oxaliplatin immediately followed by the chemotherapy drug **irinotecan** has caused overproduction of saliva and pain in the abdomen.

Nancy J. Beaulieu, RPh., BCOP

Oxycodone *see* **Opioids**

P

Paclitaxel

Definition

Paclitaxel is a drug used to treat certain types of cancer. It belongs to a category of anticancer drugs known as taxanes. Paclitaxel is available under the trade name Taxol.

Purpose

Paclitaxel is an antineoplastic agent used to treat **ovarian cancer**, **breast cancer**, non-small cell lung **carcinoma**, and AIDS-related **Kaposi's sarcoma**.

Description

Paclitaxel was approved by the Food and Drug Administration (FDA) in 1992.

Paclitaxel is a naturally occurring compound originally extracted from the bark of the Pacific yew tree (*Taxus brevifolia*). Due to high demand, paclitaxel is typically synthesized from the more abundant, naturally occurring compound 10-deacetyl baccatin III, which is extracted from the needles of yew plants. Paclitaxel belongs to a group of chemicals called taxoids. **Docetaxel**, a taxoid found in the English yew tree (*Taxus baccata*), is similar to paclitaxel in terms of chemical structure and biological action. Some researchers consider docetaxel to be preferable to paclitaxel in treating ovarian cancer because it has less severe side effects.

Paclitaxel (and docetaxel) disrupt microtubule function, inhibiting cell replication. One of the roles of normal microtubules is to aid in the replication of cells, and paclitaxel promotes the formation of microtubules that do not function properly, thus disrupting this function and inhibiting cell replication.

Paclitaxel is used in patients who have ovarian cancer carcinoma alone, and in combination with such platinum-containing drugs as **cisplatin** or carboplatin. Paclitaxel is also used to treat breast cancer that has recurred or progressed following treatment with other drugs. It is also used to treat non-small cell lung carcinoma in combination with cisplatin in cases where surgery or radiation is not possible. Paclitaxel is also used to treat AIDS-related Kaposi's sarcoma.

Recent trends in the treatment of ovarian cancer include the addition of a third drug to combination chemotherapy with carboplatin and paclitaxel; and the use of paclitaxel together with a new drug known as erlotinib (Tarceva). Erlotinib is an inhibitor of an enzyme known as tyrosine kinase, and appears to increase the antitumor effect of paclitaxel.

Recommended dosage

There is no known antidote for paclitaxel overdose, so patients should be carefully monitored during treatment for toxicity.

Paclitaxel is administered intravenously once every three weeks. Blood tests may be necessary to ensure that the bone marrow is functioning adequately to continue treatment at the recommended interval.

All patients should be pretreated prior to paclitaxel administration with **corticosteroids** and antihistamines to help prevent adverse side effects. These side effects include severe hypersensitivity to paclitaxel.

Precautions

Paclitaxel should only be used under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Special caution should be taken to monitor the toxic effects of paclitaxel, especially suppression of bone marrow function and hypersensitivity reactions. Premedication to prevent hypersensitivity reactions is recommended. Minor to severe hypersensitivity reactions are frequent and may occur within a few minutes of the start of treatment. Severe hypersensitivity

requires treatment to stop. Paclitaxel has a low therapeutic index. Certain complications will only be possible to manage if the necessary diagnostic and treatment resources are readily available.

Because paclitaxel is administered intravenously, and the site of infusion should be monitored for signs of inflammation.

Cardiac monitoring during paclitaxel administration is recommended in patients with a preexisting cardiac condition.

The occurrences of adverse effects of paclitaxel treatment in patients with significant liver dysfunction are more likely.

Paclitaxel should not be administered to patients who are known to have severe hypersensitivity to polyoxy 35 castor oil, which is a component of the treatment that helps dissolve the drug.

The safety of paclitaxel in children under 16 years of age has not been established.

Paclitaxel can cause harm to a fetus when administered to pregnant women. Only in life-threatening situations should this treatment be used during pregnancy. Women of childbearing age are advised not to become pregnant during treatment. Women should stop nursing before beginning treatment, due to the potential for serious adverse side effects in the nursing infants.

Side effects

Suppression of bone marrow function is the principal adverse side effect associated with paclitaxel treatment. Blood tests will allow a doctor to determine if there is adequate bone marrow function to begin or continue treatment. Hypersensitivity may also occur during treatment. Premedication is administered prior to treatment to help alleviate this side effect. Additional side effects, including **fever**, infection, nausea, vomiting, increase or decrease in blood pressure, **diarrhea**, **weight loss**, pain, and hair loss (alopecia) may occur.

Interactions

When used in combination with cisplatin, paclitaxel should be administered first. Paclitaxel may increase the level of **doxorubicin** (a DNA interactive anticancer drug) in the blood when used in combination. Drugs that may alter the metabolism of paclitaxel such as cyclosporine (immunosuppressant), terfenadine (antifungal), ketoconazole (antifungal), erythomycin (antibacterial), and troleandomycin (antibacterial) should be used with caution due to the potential for interactions.

KEY TERMS

10-deacetyl baccatin III—A naturally occurring compound that can be converted to paclitaxel and docetaxel.

Hypersensitivity—An abnormally sensitive reaction to a stimulus. Similar to an allergic reaction.

Microtubules—Tubular structures located in cells that help them to replicate.

Taxoid—A complex molecule that is chemically similar to paclitaxel.

Therapeutic index—A ratio of the maximum tolerated dose of a drug divided by the dose used in treatment.

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Marc Scanio
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Paget's disease of the breast

Definition

Paget's disease of the breast is a rare type of **breast cancer** that is characterized by a red, scaly lesion on the nipple and surrounding tissue (areola).

Description

Paget's disease of the breast, also called mammary Paget's disease, is a rare breast condition that is often associated with underlying breast cancer. It is believed that Paget's disease of the breast occurs when invasive **carcinoma** or intraductal carcinoma (cancer of the milk ducts) spreads through the milk ducts to the nipple.

Although in most cases the underlying breast cancer is extensive, in 10% of the cases, cancer only affects the nipple and surrounding tissue. Rarely, there is no detectable underlying breast cancer. Paget's disease located elsewhere on the body (extramammary Paget's disease) is rarely associated with an underlying invasive cancer. This type of Paget's disease, most commonly found on and around the genitals, is believed to arise directly from the cells lining certain sweat gland ducts. Possibly, the few cases of mammary Paget's disease without an underlying breast cancer have a similar origin.

Paget's disease of the breast accounts for 2% of all breast cancers. On average, women are 62 years old and men are 69 years old at diagnosis. Breast cancer rarely occurs in men.

Causes and symptoms

The causes of Paget's disease of the breast are unknown. The most common signs and symptoms of Paget's disease include redness, scaling, and flaking on and around the nipple and areola. Other symptoms include **itching**, tingling, burning, oversensitivity, or pain. The lesion may bleed or weep and open sores (ulcers) may be present.

Diagnosis

A thorough breast examination would be performed. A breast mass can be felt (palpated) in about half of the women with Paget's disease. **Mammography** and **ultrasonography** should be conducted to look for cancer within the breast that cannot be felt.

The definitive diagnosis of Paget's disease is the presence of a certain cell type, called Paget's cells, in the skin of the nipple. A tissue sample may be easily obtained by touching a microscope slide to a weeping lesion or by scraping a scaly or crusted lesion gently with a microscope slide. Alternatively, a sample of the lesion may be obtained by cutting out a small piece of nipple tissue (**biopsy**). The biopsy would be performed with local anesthetic in the physician's office. If a mass was felt, a breast biopsy would be performed.

Treatments and prognosis

Treatments

The traditional treatment of Paget's disease of the breast is to surgically remove the breast (**mastectomy**). Conservative surgery, (nipple-areolar sacrificing **lumpectomy**) in which just the nipple, areola, and underlying tissue are removed, may be sufficient in some cases. The underarm (axillary) lymph nodes are rarely sampled or removed (lymphadenectomy), unless an underlying invasive cancer is a concern.

Radiation therapy may be used as adjuvant therapy to complement the surgical treatment, and if a lumpectomy is performed, radiation must be employed. Radiation therapy uses high-energy radiation from x rays and gamma rays to kill the cancer cells. The skin in the treated area may become red and dry, and **fatigue** is also a common side effect.

Chemotherapy, also used as adjuvant therapy if an underlying invasive breast cancer is found, uses drugs to kill the cancer cells. The side effects of chemotherapy include stomach upset, vomiting, appetite loss (anorexia), hair loss (alopecia), mouth or vaginal sores, fatigue, menstrual cycle changes, premature menopause, and low white blood cell counts with an increased risk of infection.

Prognosis

As with other breast cancers, the prognosis of Paget's disease depends on the extent of the cancer and whether it has spread to the lymph nodes and other organs.

PAGET'S DISEASE ALONE The survival rate of women with Paget's disease of the breast alone is 99.5%.

PAGET'S DISEASE WITH INVASIVE BREAST CANCER The prognosis for Paget's disease and invasive cancer is based on the stage of the underlying breast cancer. Staging for breast cancer is as follows:

- Stage 1—The cancer is no larger than 2 cm (0.8 in) and no cancer cells are found in the lymph nodes.
- Stage 2—The cancer is between 2 cm and 5 cm, and the cancer has spread to the lymph nodes.

- Stage 3A—Tumor is larger than 5 cm (2 in) or is smaller than 5 cm, but has spread to the lymph nodes, which have grown into each other.
- Stage 3B—Cancer has spread to tissues near the breast, (local invasion), or to lymph nodes inside the chest wall, along the breastbone.
- Stage 4—Cancer has spread to skin and lymph nodes beyond the axilla (regional lymph nodes) or to other organs of the body.

The prognosis depends on the type and stage of cancer. Over 80% of stage I patients are cured by current therapies. Stage II patients survive overall about 70% of the time, those with more extensive lymph nodal involvement doing worse than those with disease confined to the breast. About 40% of stage III patients survive five years, and about 20% of stage IV patients do so.

Alternative and complementary therapies

Although alternative and complementary therapies are used by many cancer patients, very few controlled studies on the effectiveness of such therapies exist. Mind-body techniques such as biofeedback, visualization, meditation, and yoga, have not shown any effect in reducing cancer but they can reduce stress and lessen some of the side effects of cancer treatments.

A few studies found an association between longer survival time and a diet high in beta-carotene and fruits. Acupuncture has been found to relieve chemotherapy-induced **nausea and vomiting** and reduce pain. In some studies, mistletoe has been shown to reduce tumor size, extend survival time, and enhance immune function. Other studies have failed to show a response to mistletoe treatment.

For more comprehensive information, the patient should consult the book on complementary and alternative medicine published by the American Cancer Society listed in the Resources section.

Prevention

There are no specific factors that increase a person's risk of developing Paget's disease. Men who are at an increased risk of developing breast cancer include those who have had radiation exposure and those with Klinefelter's syndrome. Women's risk factors for breast cancer include:

- a personal history of breast cancer
- a family history of breast cancer
- alterations in certain genes (e.g. BRCA1 and BRCA2)
- changes in breast tissue (e.g. lobular carcinoma in situ or atypical hyperplasia)
- long-term exposure to estrogen (e.g. early age at first menstruation or late menopause), and possibly use of hormone replacement therapy
- exposure to diethylstilbestrol (DES) before birth
- first pregnancy after 30 years of age
- alcohol consumption

Regularly scheduled screening mammograms are recommended for all women over the age of 40 years. Those with a significant family history (one or more first-degree relatives who have been treated for breast cancer), should start annual mammograms 10 years younger than the youngest relative was when she was diagnosed, but not earlier than 35. Monthly breast self examinations and yearly clinical breast examinations are recommended for all women. Daily exercise, totalling two to four hours a week, decreases a woman's risk of breast cancer by 50% to 75%. Women with a high risk of breast cancer may take the drug **tamoxifen**, which has been shown to reduce the occurrence (or recurrence) of breast cancer. Women at a very high risk may choose to have a mastectomy to prevent breast cancer (prophylactic mastectomy).

Special concerns

Of special concern to the young woman with breast cancer is the impact that treatment will have on her fertility and **body image**. **Depression** is common. There is ongoing research investigating whether timing breast cancer surgery to coincide with the luteal phase (after

KEY TERMS

Areola—The darkened area that surrounds the nipple.

Diethylstilbestrol (DES)—A medication used between 1945 and 1970 to prevent miscarriage.

Extramammary Paget's disease—Paget's disease that is located anywhere on the body, excluding the breasts.

Luteal phase—That part of the menstrual cycle that begins after ovulation and ends at menstruation.

Mastectomy—Surgical removal of breast tissue. Mastectomy may be partial, when only some tissue is removed, or radical, when all breast tissue and adjacent tissues are removed.

QUESTIONS TO ASK THE DOCTOR

- What type of cancer do I have?
- What stage of cancer do I have?
- What is the five-year survival rate for women with this type and stage of cancer?
- Has the cancer spread?
- What are my treatment options?
- How much breast tissue will you be removing?
- Where will the scars be?
- What will my breast look like after surgery?
- When can I have breast reconstruction?
- What are the risks and side effects of these treatments?
- What medications can I take to relieve treatment side effects?
- Are there any clinical studies underway that would be appropriate for me?
- What effective alternative or complementary treatments are available for this type of cancer?
- How debilitating is the treatment? Will I be able to continue working?
- Are there any local support groups for breast cancer patients?
- What is the chance that the cancer will recur?
- Is there anything I can do to prevent recurrence?
- How often will I have follow-up examinations?

ovulation) of the menstrual cycle leads to an increased survival rate.

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Road NE, Atlanta, GA 30329. (800) ACS-2345. <http://www.cancer.org>.

Cancer Research Institute, National Headquarters. 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

National Alliance of Breast Cancer Organizations. 9 East 37th St., 10th Floor, New York, NY 10016. (888) 806-2226. <http://www.nabco.org>.

National Institutes of Health. National Cancer Institute. 9000 Rockville Pike, Bethesda, MD 20982. Cancer Information Service: (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

Y-Me Advocacy Program. 212 West Van Buren St., 5th Floor, Chicago, IL 60607. (312) 986-8338. <http://www.y-me.org>.

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Pain management

Definition

Pain management in cancer care encompasses all the actions taken to keep people with cancer as free of pain as possible. It includes pharmacological, psychological, and spiritual approaches to prevent, reduce, or stop pain sensations.

Purpose

It is estimated that more than 800,000 new cases of cancer are diagnosed each year in the United States, and 430,000 cancer victims will die. Though recent figures are hopeful and suggest a decline in both the incidence of cancer and the number of people who die from it, studies have consistently shown that at least 70% of cancer patients in the advanced stage of the disease will experi-

ence significant pain. Pain is a localized sensation ranging from mild discomfort to an unbearable, excruciating experience. It is, in its origins, a protective mechanism, designed to alert the brain to injury or disease conditions. Unfortunately, when the cause of the pain is known, such as in diagnosed cancer, and treatment is initiated, pain can often continue.

Once the message of cancer has been received and interpreted by the brain, further pain can be counter-productive. Pain can have a negative impact on a person's quality of life, causing **depression** and impeding recovery. Unrelieved pain can become a syndrome in its own right and cause a downward spiral in a person's health and outlook. Proper pain management facilitates recovery, prevents additional health complications, and improves an individual's quality of life.

Several independent studies of the relief of pain have shown that pain is often under-treated by the medical profession. For this reason, in the spring and summer of 2000, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and the American Pain Society (APS) developed standards for proper pain management.

Description

What is pain?

The treatment of pain has been a major endeavor since ancient times. By 400 B.C., the father of modern medicine, Hippocrates, had theorized that the brain, not the heart, was the controlling center of the body, and Greek anatomists had begun to identify various nerves and their purposes. The pain-relieving properties of opium were already known and were being utilized to stop suffering. Two thousand years ago, in China, acupuncture was being used to reduce pain.

Pain is the means by which the peripheral nervous system (PNS) warns the central nervous system (CNS) of injury or potential injury to the body. The CNS comprises the brain and spinal cord, and the PNS is composed of the nerves that stem from and lead into the CNS. PNS includes all nerves throughout the body except the brain and spinal cord.

A pain message is transmitted to the CNS by special PNS nerve cells called nociceptors. Nociceptors are distributed throughout the body and respond to different stimuli depending on their location. For example, nociceptors that extend from the skin are stimulated by sensations such as pressure, temperature, and chemical changes.

When a nociceptor is stimulated, neurotransmitters are released from cells. Neurotransmitters are chemicals found within the nervous system that facilitate nerve cell communication. The nociceptor transmits its signal to nerve cells within the spinal cord, which conveys the pain message to the thalamus, a specific region in the brain.

Once the brain has received and processed the pain message and coordinated an appropriate response, pain has served its purpose. The body uses natural pain killers, called endorphins, that are meant to derail further pain messages from the same source. However, these natural pain killers may not adequately dampen a continuing pain message. Also, depending on how the brain has processed the pain information, certain hormones, such as prostaglandins, may be released. These hormones enhance the pain message and play a role in immune system responses to injury, such as inflammation. Certain neurotransmitters, especially substance P and **calcitonin** gene-related peptide, actively enhance the pain message at the injury site and within the spinal cord.

It has been hypothesized that uninterrupted and unrelenting pain can induce changes in the spinal cord. In the past, intractable pain (pain that can't be managed or cured) has been treated by severing a nerve's connection to the CNS. However, the lack of any sensory information being relayed by that nerve can cause pain transmission in the spinal cord to go into overdrive, as evidenced by the phantom limb pain experienced by amputees. Evidence is accumulating that unrelenting pain or the complete lack of nerve signals increases the number of pain receptors in the spinal cord. Nerve cells in the spinal cord may also begin secreting pain-amplifying neurotransmitters independent of actual pain signals from the body. Immune chemicals, primarily cytokines, may play a prominent role in such changes.

What is cancer pain?

The majority of cancer pain results from a cancerous tumor pressing on organs, nerves, or bone. However, several studies by pain-pioneer Dr. John Bonica and others have shown that a predictable 78% of all cancer pain is indeed related to the disease, but an impressive 19% was found to be caused instead by treatment of the cancer. Three percent of all complaints of pain were unrelated to either the disease or treatment.

Cancer pain is generally divided into three categories:

- *Visceral pain*, usually caused by pressure resulting from the invasiveness of the tumor, expansion of the

hepatic capsule, or injury caused by radiation or **chemotherapy**.

- *Somatic pain* often resulting from bone metastasis.
- *Neuropathic pain*, or pain caused by the pressure of a tumor on nerves, or the trauma to nerves resulting from either radiation, chemotherapy, or surgery.

Managing cancer pain

PHARMACOLOGICAL OPTIONS General guidelines developed by the World Health Organization (WHO) for pain management apply to cancer pain management as well. These guidelines follow a three-step ladder approach:

- Mild pain is alleviated with acetominophen or non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs and acetaminophen are available as over-the-counter and prescription medications, and are frequently the initial pharmacological treatment for pain. These drugs can also be used as adjuncts to the other drug therapies, which might require a doctor's prescription. NSAIDs include aspirin, ibuprofen (Motrin, Advil, Nuprin), naproxen sodium (Aleve), and ketoprofen (Orudis KT). These drugs are used to treat pain from inflammation and work by blocking production of pain-enhancing neurotransmitters, such as prostaglandins. Acetaminophen is also effective against pain, but its ability to reduce inflammation is limited. NSAIDs and acetaminophen are effective for most forms of acute (sharp, but of a short course) pain.
- Mild to moderate pain is eased with a milder opioid medication plus acetominophen or NSAIDs. **Opioids** are both actual opiate drugs such as morphine and codeine, and synthetic drugs based on the structure of opium. This drug class includes drugs such as oxycodone, methadone, and **meperidine** (Demerol). They provide pain relief by binding to specific opioid receptors in the brain and spinal cord, and thus block the perception of pain.
- Moderate to severe pain is treated with stronger opioid drugs plus acetominophen or NSAIDs. Morphine is sometimes referred to as the "Gold Standard" of palliative care as it is not expensive, can be given starting with smaller doses and gradually increased, and is highly effective over a long period of time. It can also be administered orally (by mouth), rectally, or by injection. A newer method of administering morphine involves a patient-controlled delivery system implanted in the covering of the spinal cord. Researchers in North Carolina reported in late 2003 that the new system not only provided more effective pain relief, but also lowered the patients' use of morphine and the complications associated with long-term use of morphine. In general, the development of implantable pumps has greatly improved pharmacological approaches to pain management.

Although antidepressant drugs were developed to treat depression, they are also effective in combating chronic headaches, cancer pain, and pain associated with nerve damage. Antidepressants shown to have analgesic (pain reducing) properties include **amitriptyline** (Elavil), trazodone (Desyrel), and imipramine (Tofranil). Anticonvulsant drugs share a similar background with antidepressants. Developed to treat epilepsy, anticonvulsants were found to relieve pain as well. Drugs such as **phenytoin** (Dilantin) and **carbamazepine** (Tegretol) are prescribed to treat the pain associated with nerve damage.

Close monitoring of the effects of pain medications is required in order to assure that adequate amounts of medication are given to produce the desired pain relief. When a person is comfortable with a certain dosage of medication, oncologists typically convert to a long-acting version of that medication. Transdermal fentanyl patches (Duragesic) are a common example of an long-acting opioid drug often used for cancer pain management. A patch containing the drug is applied to the skin where the drug is continuously absorbed by the body, usually for three days. Pumps are also available that provide an opioid medication upon demand when the person is experiencing pain. By pressing a button, they can release a set dose of medication into an intravenous solution or an implanted catheter. Another mode of administration involves implanted catheters that deliver pain medication directly to the spinal cord. Delivering drugs in this way can reduce side effects and increase the effectiveness of the drug. Research is underway to develop toxic substances that act selectively on nerve cells that carry pain messages to the brain, killing these selected cells, and thus stopping transmission of the pain message.

NON-PHARMACOLOGICAL OPTIONS Pain treatment options that do not involve drugs are often used as adjuncts to, rather than replacements for, drug therapy. One of the benefits of non-drug therapies is that an individual can take a more active stance against pain. Relaxation techniques, such as yoga and meditation, are used to shift the focus of the brain away from the pain, decrease muscle tension, and reduce stress. Tension and stress can also be reduced through biofeedback, in which an individual consciously attempts to modify skin temperature, muscle tension, blood pressure, and heart rate. A group of researchers in New York reported in 2003 that the hypnotic-like approaches—particularly imagery, relaxation techniques, and hypnotic suggestion—appear to be more effective in managing pain than other behavioral approaches.

KEY TERMS

Acute—A short-term pain in response to injury or other stimulus that resolves when the injury heals or the stimulus is removed.

Chemotherapy—The treatment of infections or malignant diseases by drugs that act selectively on the cause of the disorder, but which may have substantial side effects.

Chronic—Pain that endures beyond the term of an injury or painful stimulus. Also refers to cancer pain, pain from a chronic or degenerative disease, and pain from an unidentified cause.

CNS or central nervous system—The part of the nervous system that includes the brain and the spinal cord.

Hepatic capsule—The membranous bag enclosing the liver.

Iatrogenic—Resulting from the activity of the physician.

Metastasis—A secondary malignant tumor (one that has spread from a primary cancer to affect other parts of the body.

Neuropathy—Nerve damage.

Neurotransmitter—Chemicals within the nervous system that transmit information from or between nerve cells.

Nociceptor—A nerve cell capable of sensing pain and transmitting a pain signal.

Non-pharmacological—Therapy that does not involve drugs.

Palliative—Serving to relieve or alleviate the symptoms of a disease or disorder without curing the disease.

Pharmacological—Therapy that relies on drugs.

PNS or peripheral nervous system—Nerves that are outside of the brain and spinal cord.

Radiation—A treatment for cancer (and occasionally other diseases) by x rays or other sources of radioactivity, both of which produce ionizing radiation. The radiation, as it passes through diseased tissue, destroys or slows the development of abnormal cells.

Stimulus—A factor capable of eliciting a response in a nerve.

Virtual reality—The creation of a convincing environment by computer technology, displayed either on a computer screen or viewed through special stereoscopic goggles. Virtual reality is primarily a visual and auditory experience. It appears to be a useful approach to pain management in children.

Participating in normal activities and exercising can also help control pain levels. Through physical therapy, an individual learns beneficial exercises for reducing stress, strengthening muscles, and staying fit. Regular exercise has been linked to production of endorphins, the body's natural pain killers.

Acupuncture involves the insertion of small needles into the skin at key points. The acupuncturist will usually stimulate points on the ear when treating cancer pain. Acupressure uses these same key points, but involves applying pressure rather than inserting needles. Both of these methods may work by prompting the body to release endorphins. Applying heat or being massaged are very relaxing and help reduce stress. Transcutaneous electrical nerve stimulation (TENS) applies a small electric current to certain parts of nerves, potentially interrupting pain signals and inducing release of endorphins. To be effective, use of TENS should be medically supervised.

A new method for managing pain in children with cancer is virtual reality, which works by distracting the child's attention from the pain and accompanying anxiety. Virtual reality has been used successfully in the treatment of anxiety disorders, and shows great promise in treating children suffering from cancer pain. Larger-scale studies are under way as of late 2003.

Preparation

Assessment of cancer pain is absolutely essential to good pain management. Pain scales or questionnaires are sometimes used to attach an objective measure to a subjective experience. Objective measurements allow health care workers a better understanding of the pain being suffered by the patient. Pain has been called "the fifth vital sign," (temperature, pulse, respiration and blood pressure being the other four vital signs), by the Veterans Administration. Evaluation also includes physical examinations and diagnostic tests to determine underlying cause of the pain. Some evaluations require assessments from several viewpoints, including neurology, psychiatry and psychology, and physical therapy.

Risks

Owing to toxicity over the long term, even non-prescription drugs must be carefully monitored in chronic pain management. NSAIDs have the well-known side effect of causing gastrointestinal bleeding, and long-term use of acetaminophen has been linked to kidney and liver damage. Other drugs, especially narcotics, have side effects such as constipation, drowsiness, and nausea. Sedation can often be reduced by the timing of when medication is taken (such as at bedtime), and constipation can be reduced by increasing the amount of fruits, vegetables, and whole-grain foods in the diet, or by the use of **laxatives**, stool softeners, or even enemas. Serious side effects can also accompany antidepressants and anticonvulsants, which may discourage or prevent their use depending upon the circumstances. These side effects include mood swings, confusion, bone thinning, cataract formation, increased blood pressure, and other problems.

Non-pharmacological therapies carry little or no risks. However, it is advised that individuals recovering from serious illness or injury consult with their health care providers or physical therapists before making use of adjunct therapies. Invasive procedures carry risks similar to other surgical procedures, such as infection, reaction to anesthesia, iatrogenic injury (injury as a result of treatment), and heart failure.

A traditional concern about narcotics use has been the risk of promoting addiction or tolerance. As narcotic use continues over time, as in terminal cancer, the body becomes accustomed to the drug and adjusts normal functions to accommodate to its presence. Therefore, to elicit the same level of action, it is necessary to increase dosage over time. Tolerance can be defined as a gradual lessening of the effectiveness of an opioid drug from continued use.

Many studies involving cancer patients have indicated that proper dosage of narcotic medication does not create an addiction to it. A major concern for many cancer patients though, is that the medication will stop working for them. Evidence suggests this is not true. A simple increase in the dose will usually cause the medication to relieve pain again. One of the biggest dangers is abruptly stopping an opioid medication or reducing the dose, as the person can then go into withdrawal, a potentially serious medical condition characterized by agitation, rapid heart rate, profuse sweating and sleeplessness.

However, physical dependence is different from psychological addiction. Physical dependence is characterized by discomfort if drug administration suddenly stops, while psychological addiction is characterized by an overpowering craving for the drug for reasons other than pain relief. Psychological addiction is a very real and necessary concern in some instances, but it should not interfere with a genuine need for narcotic pain relief.

QUESTIONS TO ASK THE DOCTOR

- Does my type of cancer usually cause pain, and if so, how will the pain be treated?
- Does the radiation or chemotherapy that I may have cause pain?
- What are the side-effects of the medications you will order?
- What things can I do to help with my pain management?
- Does the pain necessarily mean that the cancer is getting worse?

Normal results

Effective application of pain management techniques reduces or eliminates cancer pain. This treatment can improve an individual's quality of life and aid in recovery.

Perhaps the best measure of the results of pain management for cancer patients would be the fulfillment of the recently developed Bill of Rights for Cancer Pain. It is as follows:

- You have the right to be believed about the severity of your pain.
- You have the right to have your pain controlled.
- You have the right to have pain resulting from treatments and procedures prevented, or at least minimized.
- You have the right to be treated with respect at all times when you need medication; to not be treated like a drug abuser.

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American Pain Society. 4700 West Lake Ave., Glenview, IL 60025. (847) 375-4715. <http://www.ampainsoc.org>.

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National Chronic Pain Outreach Association, Inc. PO Box 274, Millboro, VA 24460-9606. (540) 997-5004.

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Pamidronate *see* **Bisphosphonates**

Pancreatic cancer, endocrine

Definition

Endocrine pancreatic cancer is a disease in which cancerous cells originate within the tissues of the pancreas that produce hormones.

Description

The pancreas is a six- to eight-inch long, slipper-shaped gland located in the abdomen. It lies behind the stomach, within a loop formed by the small intestine. Other nearby organs include the gallbladder, spleen, and liver. The pancreas has a wide end (head), a narrow end (tail), and a middle section (body). A healthy pancreas is important for normal food digestion and plays a critical role in the body's metabolic processes. The pancreas has two main functions, each performed by distinct types of tissue. The exocrine tissue secretes fluids into the other organs of the digestive system, while the endocrine tissue secretes substances that are circulated in the bloodstream. The exocrine pancreas makes up the vast majority of the gland; it produces pancreatic juices containing enzymes that help break down proteins and fatty food. The endocrine tissue of the pancreas makes up only 2% of the gland's total mass. It consists of small patches of cells that produce hormones (like insulin) that control how the body stores and uses nutrients. These patches are called islets (islands) of Langerhans or islet cells and are interspersed evenly throughout the pancreas. Each islet contains approximately 1,000 endocrine cells and a dense network of capillaries (tiny blood vessels), which allows immediate entry of hormones into the circulatory system.

Pancreatic tumors are classified as either exocrine or endocrine tumors depending on which type of tissue they arise from within the gland. Endocrine tumors of the pancreas are very rare, accounting for only 5% of all pancreatic cancers. The majority of endocrine pancreatic tumors are functional **adenocarcinomas** that overproduce a specific hormone. There are several types of islet cells and each produces its own hormone or peptide (small protein molecule). Functional endocrine tumors are named after the hormone they secrete. Insulinoma is the most common tumor of the endocrine pancreas. Patients with this disease usually develop hypoglycemia due to increased insulin production that leads to abnormally low blood sugar levels. Gastrinoma, a disease in which gastrin (hormone which stimulates stomach acid production) is overproduced, causes multiple ulcers in the upper gastrointestinal (GI) tract. Gastrinoma was first described in patients with a rare form of severe peptic ulcer disease known as **Zollinger-Ellison syndrome** (ZES). The less common glucagonoma causes mild diabetes due to excess glucagon (hormone which stimulates glucose production) secretion. Other rare islet cell tumors include vipoma (vasoactive intestinal peptide) and somatostatinoma. Nonfunctional pancreatic endocrine tumors are not associated with an excess production of any hormone and can be difficult to distinguish from exocrine pancreatic cancer. Cancers of the endocrine pancreas are relatively slow-growing compared to the more common ductal adenocarcinomas of the exocrine pancreas.

Demographics

Between one and four cases of insulinoma occur per million people per year, and 90% of these tumors are benign. They occur mostly between the ages of 50 and

60 and affect men and women equally. Less than three cases of gastrinoma per million people are diagnosed each year, but it is the most common functional islet cell tumor in patients with multiple endocrine tumors, a condition known as multiple endocrine neoplasia (MEN) syndrome. Vipoma and glucagonoma are even rarer and they occur more frequently in women. Somatostatinoma is exceedingly uncommon, and less than 100 cases have been reported worldwide. Nonfunctional islet cell cancers account for approximately one-third of all cancers of the endocrine pancreas, and the majority of these are malignant.

Causes and symptoms

There are no known causes of islet cell cancer, but a small percentage of cases occur due to hereditary syndromes such as MEN. This is a condition that frequently causes more than one tumor in several endocrine glands, such as the parathyroid and pituitary, in addition to the islet cells of the pancreas. Twenty-five percent of gastrinomas and less than 10% of insulinomas occur in MEN patients. Von Hippel-Lindau (VHL) syndrome is another genetic disorder that causes multiple tumors, and 10% to 15% of VHL patients will develop islet cell cancer.

Symptoms vary among the different islet cell cancer types. Insulinoma causes repeated episodes of hypoglycemia, sweating, and tremors, while patients with gastrinoma have inflammation of the esophagus, epigastric pain, multiple ulcers, and possibly **diarrhea**. Symptoms of glucagonoma include a distinctive skin rash, inflammation of the stomach, glucose intolerance, **weight loss**, weakness, and **anemia** (less common). Patients with vipoma have episodes of profuse, watery diarrhea, even after fasting. Somatostatinoma causes mild diabetes, diarrhea/steatorrhea (fatty stools), weight loss, and gallbladder disease. Nonfunctional endocrine tumors frequently produce the same symptoms as cancer of the exocrine pancreas such as abdominal pain, jaundice, and weight loss.

Diagnosis

A thorough physical exam is usually performed when a patient visits a doctor with the above symptoms; however, functional endocrine tumors of the pancreas tend to be small and are not detected by palpating the abdomen. Once other illnesses such as infection are ruled out, the doctor will order a series of blood and urine tests. The functional endocrine tumors can be identified through increased levels of hormone in the bloodstream.

Functional endocrine tumors can occur in multiple sites in the pancreas and are often small (less than 1 cm), making them difficult to diagnose. Nonfunctional tumors tend to be larger, which makes them difficult to distinguish from tumors of the exocrine pancreas. Methods such as **computed tomography** (CT) scan and **magnetic resonance imaging** (MRI) are used to take pictures of the internal organs and allow the doctor to determine whether a tumor is present. Somatostatin receptor scintigraphy (trade name OctreoScan) is an imaging system used to localize endocrine tumors, especially gastrinomas and somatostatinomas. Endoscopic ultrasound (EUS) is a more sensitive technique that may be used if a CT scan fails to detect a tumor. Endocrine tumors usually have many blood vessels, so **angiography** may be useful in the doctor's assessment and staging of the tumor. Surgical exploration is sometimes necessary in order to locate very small tumors that occur in multiple sites. These techniques also help the doctor evaluate how far the tumor has spread. A **biopsy** can be taken to confirm diagnosis, but more often, doctors look at the size and local invasion of the tumor in order to plan a treatment strategy.

Treatment team

Patients with islet cell cancer are cared for by a number of specialists from different disciplines. Medical oncologists, gastroenterologists, radiologists, and surgeons all interact with the patient to develop an appropriate treatment plan. Endocrinologists play an important role in helping patients with diabetes maintain steady blood sugar levels. Much of the treatment of islet cell cancer focuses on relieving symptoms of the tumor through medication that inhibits hormone overproduction. It is best for patients to work with doctors who are experienced in treating this rare form of cancer.

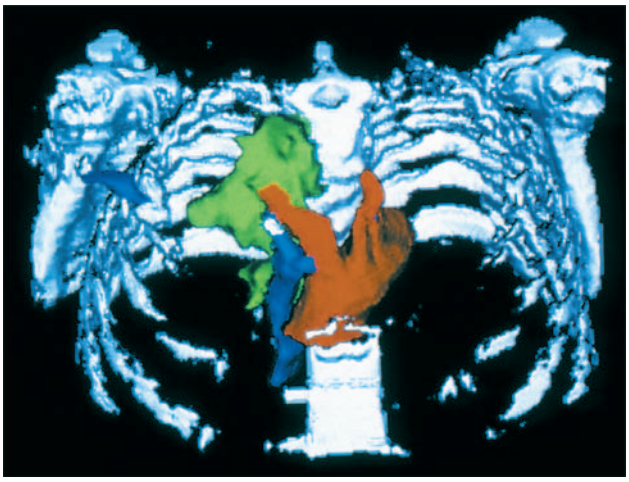
Clinical staging, treatments, and prognosis

Staging

The staging system for islet cell cancer is still evolving, but the tumors typically fall into three categories: cancers that arise in one location within the pancreas, cancers that arise in several locations within the pancreas, and cancers that have spread to nearby lymph nodes or to other organs in the body.

Treatments

Surgery is the only curative method for islet cell cancers, and studies have shown that an aggressive surgical approach can improve survival and alleviate symptoms of the disease. As with most forms of cancer, the earlier it is diagnosed, the greater the chance



Colorized computed tomography (CT) scan showing the location of a cancerous tumor of the pancreas (green). *(Copyright Clinique Ste Catherine/CNRI, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

for survival. With the exception of insulinoma, the majority of islet cell tumors are malignant at the time of diagnosis, and more than half are metastatic. However, surgery and **chemotherapy** have been shown to improve the outcome of patients even if they have metastatic disease. Surgery may include partial or total removal of the pancreas, and in patients with gastrinoma, the stomach may be removed as well. Streptozocin, **doxorubicin**, and 5-fluorouracil (5-FU, or fluorouracil) are chemotherapeutic agents commonly used in the treatment of islet cell cancer. Patients may experience **nausea and vomiting**, as well as kidney toxicity, from streptozocin, and bone marrow suppression from doxorubicin. Hormone therapy is used to relieve the symptoms of functional tumors by inhibiting excess hormone production. Other techniques may be used to block blood flow to the liver in an attempt to kill the cancer cells that have spread there. Abdominal pain, nausea, vomiting, and **fever** may result from this type of treatment. Radiation has little if any role in the treatment of islet cell cancer.

Prognosis

Islet cell cancers overall have a more favorable prognosis than cancers of the exocrine pancreas, and the median survival from diagnosis is three-and-half years. This is mainly due to their slow-growing nature. Insulinomas have a five-year survival rate of 80% and gastrinomas have 65%. When malignant, islet cell cancers do not generally respond well to chemotherapy, and the treatment is mainly palliative. Most patients with **metastasis** do not survive five years. Islet cell cancer tends to spread to the surrounding lymph nodes, stomach, small intestine, and liver.

KEY TERMS

Adenocarcinoma—A malignant tumor that arises within the tissues of a gland and retains its glandular structure.

Angiography—Diagnostic technique used to study blood vessels in a tumor.

Biopsy—Removal and microscopic examination of cells to determine whether they are cancerous.

Chemotherapy— Drug treatment administered to kill cancerous cells.

Endocrine—Refers to glands that secrete hormones circulated in the bloodstream.

Endoscopic Ultrasonography (EUS)—Diagnostic imaging technique where an ultrasound probe is inserted down a patient's throat to determine if a tumor is present.

Gastrinoma—Tumor that arises from the gastrin-producing cells in the pancreas.

Insulinoma—Tumor that arises from the insulin-producing cells in the pancreas.

Islets of Langerhans—Clusters of cells in pancreas that make up the endocrine tissue.

Coping with cancer treatment

Patients should discuss with their doctors any side effects they experience from treatment. Many drugs are available to relieve nausea and vomiting associated with cancer treatments and for combating **fatigue**. Insulin may be prescribed if patients develop diabetes as a result of partial or total removal of their pancreas. Special diets or fluids may be recommended if patients have more than one digestive organ removed. These patients may require intravenous feeding after surgery until they recover.

Clinical trials

Because this is such a rare disease, relatively few **clinical trials** are available to people with islet cell cancer. Most are investigating the efficacy of new chemotherapeutic drugs or combinations of drugs and biological therapies. R115777 is an agent being tested in combination with **trastuzumab** (Herceptin) for patients with advanced or metastatic adenocarcinoma. Two new drugs that are antineoplastons, A10 and

QUESTIONS TO ASK THE DOCTOR

- What type of islet cell cancer do I have?
- Do you have experience in treating this form of cancer?
- Is my tumor benign or malignant?
- What is my prognosis?
- Can my tumor be removed by surgery?
- What medication will I need to take?
- Am I at risk for developing other endocrine tumors?
- Is there a clinical trial I can participate in?
- Is there a support group available?

AS2-1, are being examined together as a treatment regimen for patients with metastatic or incurable **neuroendocrine tumors**. Patients should ask their doctors whether they qualify for these or other clinical trials.

Prevention

There are no known risk factors associated with sporadic islet cell cancer. Therefore, it is not clear how to prevent its occurrence. Individuals with MEN syndrome or VHL, however, have a genetic predisposition to developing islet cell cancer should be screened regularly in an effort to catch the disease early.

Special concerns

Many patients find it helpful to join support groups after being diagnosed with cancer. Discussing the condition with others who are experiencing a similar situation may help to relieve anxiety and **depression**, which are often associated with cancer and its treatment. Medication may also be prescribed to alleviate depression. Patients should learn as much as they can about their illness and find out what their treatment options are. It is important for patients to remember that each cancer has unique characteristics and responds differently to treatment depending on those characteristics.

See also Carcinoid tumors, gastrointestinal; Chemoembolization; Complementary cancer therapies; Endocrine system tumors; Familial cancer syndromes; Pancreatic cancer, exocrine; Upper gastrointestinal endoscopy.

Resources

PERIODICALS

Anderson, M.A., et. al. "Endoscopic Ultrasound is Highly Accurate and Directs Management of Patients With Neuroendocrine Tumors of the Pancreas." *American Journal of Gastroenterology* 95, no. 9 (September 2000): 2271–7.

Hellman, Per, et. al. "Surgical Strategy for Large or Malignant Endocrine Pancreatic Tumors." *World Journal of Surgery* 24 (2000): 1353–60.

ORGANIZATIONS

National Cancer Institute. 9000 Rockville Pike, Bldg.31, Rm.10A16, Bethesda, MD, 20892 (800) 422-6237. <http://www.nci.nih.gov>.

National Familial Pancreas Tumor Registry. The Johns Hopkins Hospital. 600 North Wolfe St., Baltimore, MD 21287-6417. (410) 377-7450.

National Organization for Rare Disorders. 100 Route 37, PO Box 8923. New Fairfield, CT 06812. (203) 746-6518. <http://www.nord-rdb.com/~orphan>.

OTHER

"Islet Cell Carcinoma." *CancerNet PDQ*. May 2001. [cited July 19, 2001]. <http://www.cancernet.nci.nih.gov>.

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Pancreatic cancer, exocrine

Definition

Exocrine pancreatic cancer is a disease in which cancerous cells originate within the tissues of the pancreas that produce digestive juices.

Description

The pancreas is a six- to eight-inch long, slipper-shaped gland located in the abdomen. It lies behind the stomach, within a loop formed by the small intestine. Other nearby organs include the gallbladder, spleen, and liver. The pancreas has a wide end (head), a narrow end (tail), and a middle section (body). A healthy pancreas is important for normal food digestion and also plays a critical role in the body's metabolic processes. The pancreas has two main functions, and each are performed by distinct types of tissue. The exocrine tissue makes up the vast majority of the gland and

secretes fluids into the other organs of the digestive system. The endocrine tissue secretes hormones (like insulin) that are circulated in the bloodstream, and these substances control how the body stores and uses nutrients. The exocrine tissue of the pancreas produces pancreatic (digestive) juices. These juices contain several enzymes that help break down proteins and fatty foods. The exocrine pancreas forms an intricate system of channels or ducts, which are tubular structures that carry pancreatic juices to the small intestine where they are used for digestion.

Pancreatic tumors are classified as either exocrine or endocrine tumors depending on which type of tissue they arise from within the gland. Ninety-five percent of pancreatic cancers occur in the tissues of the exocrine pancreas. Ductal adenocarcinomas arise in the cells that line the ducts of the exocrine pancreas and account for 80% to 90% of all tumors of the pancreas. Unless specified, nearly all reports on pancreatic cancer refer to ductal adenocarcinomas. Less common types of pancreatic exocrine tumors include acinar cell **carcinoma**, cystic tumors that are typically benign but may become cancerous, and papillary tumors that grow within the pancreatic ducts. Pancreatoblastoma is a very rare disease that primarily affects young children. Two-thirds of pancreatic tumors occur in the head of the pancreas, and tumor growth in this area can lead to the obstruction of the nearby common bile duct that empties bile fluid into the small intestine. When bile cannot be passed into the intestine, patients may develop yellowing of the skin and eyes (jaundice) due to the buildup of bilirubin (a component of bile) in the bloodstream. Tumor blockage of bile or pancreatic ducts may also cause digestive problems since these fluids contain critical enzymes in the digestive process. Depending on their size, pancreatic tumors may cause abdominal pain by pressing on the surrounding nerves. Because of its location deep within the abdomen, pancreatic cancer often remains undetected until it has spread to other organs such as the liver or lung. Pancreatic cancer tends to rapidly spread to other organs, even when the primary (original) tumor is relatively small.

Demographics

Though pancreatic cancer accounts for only 3% of all cancers, it is the fifth most frequent cause of cancer deaths. In 2001, an estimated 29,200 new cases of pancreatic cancer will be diagnosed in the United States. Pancreatic cancer is primarily a disease associated with advanced age, with 80% of cases occurring between the ages of 60 and 80. Men are almost twice as likely to develop this disease than women. Countries with the highest frequencies of pancreatic cancer include the U.S., New Zealand, Western European nations, and Scandinavia. The lowest occurrences of the disease are reported in India, Kuwait and Singapore. African Americans have the highest rate of pancreatic cancer of any ethnic group worldwide. Whether this difference is due to diet or environmental factors remains unclear.

Causes and symptoms

Although the exact cause for pancreatic cancer is not known, several risk factors have been shown to increase susceptibility to this particular cancer, the greatest of which is cigarette smoking. Approximately one-third of pancreatic cancer cases occur among smokers. People who have diabetes develop pancreatic cancer twice as often as non-diabetics. Numerous studies suggest that a family history of pancreatic cancer is another strong risk factor for developing the disease, particularly if two or more relatives in the immediate family have the disease. Other risk factors include chronic (long-term) inflammation of the pancreas (pancreatitis), diets high in fat, and occupational exposure to certain chemicals such as petroleum.

Pancreatic cancer often does not produce symptoms until it reaches an advanced stage. Patients may then present with the following signs and symptoms:

- upper abdominal and/or back pain
- jaundice
- weight loss
- loss of appetite (anorexia)
- diarrhea
- weakness
- nausea

These symptoms may also be caused by other illnesses; therefore, it is important to consult a doctor for an accurate diagnosis.

Diagnosis

Pancreatic cancer is difficult to diagnose, especially in the absence of symptoms, and there is no current screening method for early detection. The most sophisticated techniques available often do not detect very small tumors that are localized (have not begun to spread). At advanced stages where patients show symptoms, a number of tests may be performed to confirm diagnosis and to assess the stage of the disease. Approximately half of all pancreatic cancers are metastatic (have spread to other sites) at the time of diagnosis.

The first step in diagnosing pancreatic cancer is a thorough medical history and complete physical examination. The abdomen will be palpated to check for fluid

accumulation, lumps, or masses. If there are signs of jaundice, blood tests will be performed to rule out the possibility of liver diseases such as hepatitis. Urine and stool tests may be performed as well.

Non-invasive imaging tools such as **computed tomography** (CT) scans and **magnetic resonance imaging** (MRI) can be used to produce detailed pictures of the internal organs. CT is the tool most often used to diagnose pancreatic cancer, as it allows the doctor to determine if the tumor can be removed by surgery or not. It is also useful in staging a tumor by showing the extent to which the tumor has spread. During a CT scan, patients receive an intravenous injection of a contrast dye so the organs can be visualized more clearly. MRI may be performed instead of CT if a patient has an allergy to the CT contrast dye. In some cases where the tumor is impinging on blood vessels or nearby ducts, MRI may be used to generate an image of the pancreatic ducts.

If the doctor suspects pancreatic cancer and no visible masses are seen with a CT scan, a patient may undergo a combination of invasive tests to confirm the presence of a pancreatic tumor. Endoscopic ultrasound (EUS) involves the use of an ultrasound probe at the end of a long, flexible tube that is passed down the patient's throat and into the stomach. This instrument can detect a tumor mass through high frequency sound waves and echoes. EUS can be accompanied by fine needle aspiration (FNA), where a long needle, guided by the ultrasound, is inserted into the tumor mass in order to take a **biopsy** sample. **Endoscopic retrograde cholangiopancreatography** (ERCP) is a technique often used in patients with severe jaundice because it enables the doctor to relieve blockage of the pancreatic ducts. The doctor, guided by endoscopy and x rays, inserts a small metal or plastic stent into the duct to keep it open. During ERCP, a biopsy can be done by collecting cells from the pancreas with a small brush. The cells are then examined under the microscope by a pathologist, who determines the presence of any cancerous cells.

In some cases, a biopsy may be performed during a type of surgery called **laparoscopy**, which is done under general anesthesia. Doctors insert a small camera and instruments into the abdomen after a minor incision is made. Tissue samples are removed for examination under the microscope. This procedure allows a doctor to determine the extent to which the disease has spread and decide if the tumor can be removed by further surgery.

An **angiography** is a type of test that studies the blood vessels in and around the pancreas. This test may be done before surgery so that the doctor can determine the extent to which the tumor invades and interacts with the blood vessels within the pancreas. The test requires local anesthesia and a catheter is inserted into the patient's upper thigh. A dye is then injected into blood vessels that lead into the pancreas, and x rays are taken.

As of April 2001, doctors at major cancer research institutions such as Memorial Sloan-Kettering Cancer Center in New York were investigating CT angiography, an imaging technique that is less invasive than angiography alone. CT angiography is similar to a standard CT scan, but allows doctors to take a series of pictures of the blood vessels that support tumor growth. A dye is injected as in a CT scan (but at rapid intervals) and no catheter or sedation is required. A computer generates 3D images from the pictures that are taken, and the information is gathered by the surgical team who will develop an appropriate strategy if the patient's disease can be operated on.

Treatment team

Pancreatic cancer is a complex disease that involves specialists from a variety of medical disciplines. Patients are likely to interact with medical oncologists, gastroenterologists, radiologists, and surgeons to develop a suitable treatment plan. Treatment plans vary depending on the stage of the disease and the overall health of the patient. Cancers of the pancreas frequently cause intense pain by pressing on the surrounding network of nerves in the abdomen; therefore, anesthesiologists who specialize in pain management may play a role in making a patient more comfortable. Obstruction of the intestine or bowel can also be a cause of pain, but is usually relieved through surgery. Patients receiving **chemotherapy** meet with oncologists who determine the dose schedule and oncology nurses who administer the chemotherapy. Patients who undergo partial or total removal of their pancreas may develop diabetes, and an endocrinologist will prescribe insulin or other medication to help them manage this condition. It is important for patients to get proper nutrition during any treatment for cancer. Patients may wish to consult a nutritionist or dietician to assist them (this may require oral replacement of digestive enzymes).

Clinical staging, treatments, and prognosis

Staging

After cancer of the pancreas has been diagnosed, doctors typically use a TNM staging system to classify the tumor based on its size and the degree to which it has spread to other areas in the body. T indicates the size and local advancement of the primary tumor. Since cancers often invade the lymphatic system before

spreading to other organs, regional lymph node involvement (N) is an important factor in staging. M indicates whether the tumor has metastasized (spread) to distant organs. In stage I, the tumor is localized to the pancreas and has not spread to surrounding lymph nodes or other organs. Stage II pancreatic cancer has spread to nearby organs such as the small intestine or bile duct, but not the surrounding lymph nodes. Stage III indicates lymph node involvement, whether the cancer has spread to nearby organs or not. Stage IVA pancreatic cancer has spread to organs near the pancreas such as the stomach, spleen, or colon. Stage IVB is a cancer that has spread to distant sites (liver, lung). If pancreatic cancer has been treated with success and then appears again in the pancreas or in other organs, it is referred to as recurrent disease.

Treatments

Treatment of pancreatic cancer will depend on several factors, including the stage of the disease and the patient's age and overall health status. A combination of therapies is often employed in the treatment of this disease to improve the patient's chances for survival. Surgery is used whenever possible and is the only means by which cancer of the pancreas can be cured. However, less than 15% of pancreatic tumors can be removed by surgery. By the time the disease is diagnosed (usually at Stage III), therapies such as radiation and chemotherapy or both are used in addition to surgery to relieve a patient's symptoms and enhance quality of life. For patients with metastatic disease, chemotherapy and radiation are used mainly as palliative (pain-alleviating) treatments.

SURGERY Three types of surgery are used in the treatment of pancreatic cancer, depending on what section of the pancreas the tumor is located in. A Whipple procedure removes the head of the pancreas, part of the small intestine and some of the surrounding tissues. This procedure is most common since the majority of pancreatic cancers occur in the head of the organ. A total pancreatectomy removes the entire pancreas and the organs around it. Distal pancreatectomy removes only the body and tail of the pancreas. Chemotherapy and radiation may precede surgery (neoadjuvant therapy) or follow surgery (adjuvant therapy). Surgery is also used to relieve symptoms of pancreatic cancer by draining fluids or bypassing obstructions. Side effects from surgery can include pain, weakness, **fatigue**, and digestive problems. Some patients may develop diabetes or malabsorption as a result of partial or total removal of the pancreas.

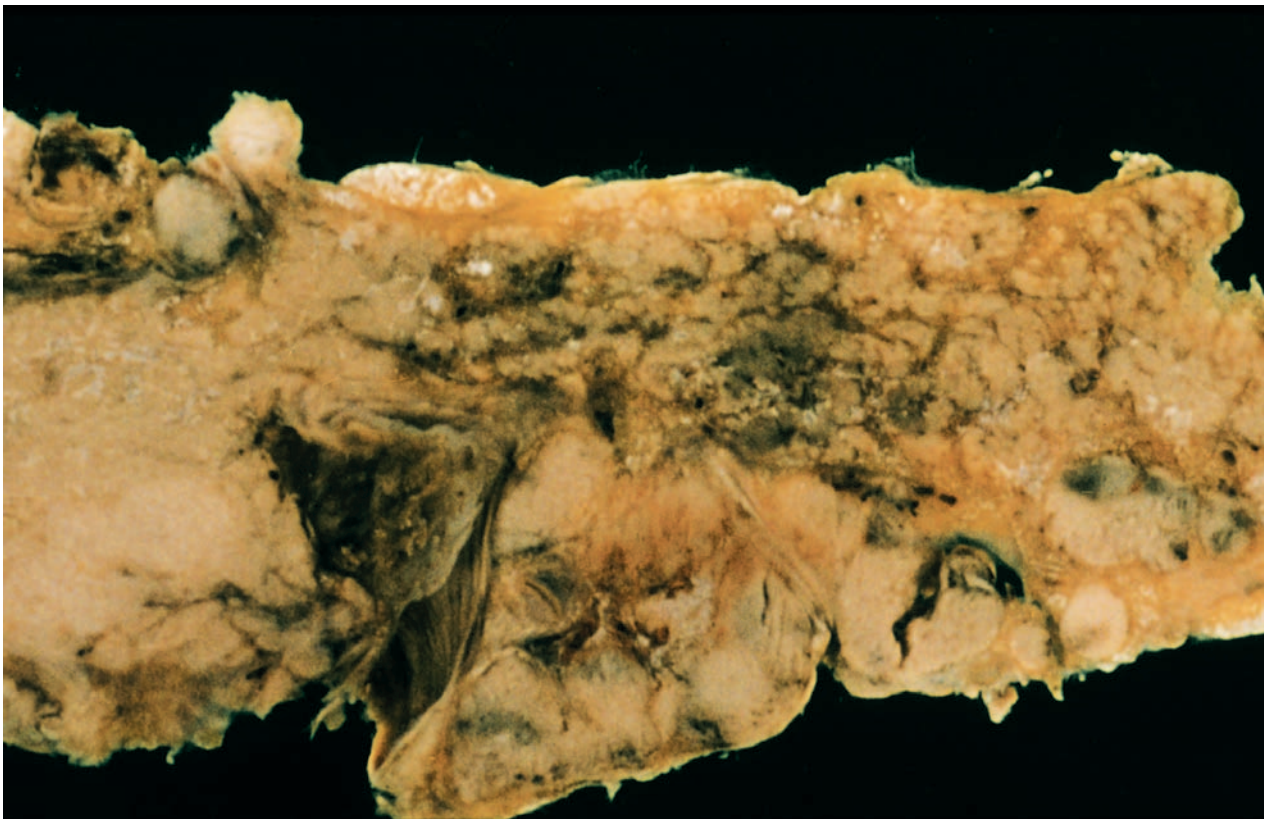
RADIATION THERAPY **Radiation therapy** is sometimes used to shrink a tumor before surgery or to remove remaining cancer cells after surgery. Radiation may also be used to relieve pain or digestive problems caused by the tumor if it cannot be removed by surgery. External radiation therapy refers to radiation applied externally to the abdomen using a beam of high-energy x rays. High-dose intraoperative radiation therapy is sometimes used during surgery on tumors that have spread to nearby organs. Internal radiation therapy refers to the use of small radioactive seeds implanted in the tumor tissue. The seeds emit radiation over a period of time to kill tumor cells. Radiation treatment may cause side effects such as fatigue, tender or itchy skin, nausea, vomiting, and digestive problems.

CHEMOTHERAPY Chemotherapeutic agents are powerful drugs that are used to kill cancer cells. They are classified according to the mechanism by which they induce cancer cell death. Multiple agents are often used to increase the chances of tumor cell death. **Gemcitabine** is the standard drug used to treat pancreatic cancers and can be used alone or in combination with other drugs, such as 5-fluorouracil (5-FU, or fluorouracil). Other drugs are being tested in combination with gemcitabine in several ongoing **clinical trials**, specifically **irinotecan** (CPT-11) and **oxaliplatin**. Chemotherapy may be administered orally or intravenously in a series of doses over several weeks. During treatment, patients may experience fatigue, nausea, vomiting, hair loss (alopecia), and mouth sores, depending on which drugs are used.

BIOLOGICAL TREATMENTS Numerous vaccine treatments are being developed in an effort to stimulate the body's immune system into attacking cancer cells. This is also referred to as immunotherapy. Another type of biological treatment involves using a targeted monoclonal antibody to inhibit the growth of cancer cells. The antibody is thought to bind to and neutralize a protein that contributes to the growth of the cancer cells. Investigational treatments such as these may be considered by patients with metastatic disease who would like to participate in a clinical trial. Biological treatments typically cause flu-like symptoms (chills, **fever**, loss of appetite) during the treatment period.

Prognosis

Unfortunately, cancer of the pancreas is often fatal, and median survival from diagnosis is less than six months, while the five-year survival rate is 4%. This is mainly due to the lack of screening methods available for early detection of the disease. Yet, even when localized tumors can be removed by surgery, patient survival after five years is only 10% to 15%. These statistics demonstrate the aggressive nature of most pancreatic cancers and their tendency to recur. Pancreatic cancers tend to be resistant to radiation and chemotherapy and



Carcinoma of the head of the pancreas. Tumors appear as gritty, gray, hard nodules, invading the adjacent gland. *(Copyright Biophoto Associates, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

these modes of treatment are mainly used to relieve pain and tumor burden.

Alternative and complementary therapies

Acupuncture or hypnotherapy may be used in addition to standard therapies to help relieve the pain associated with pancreatic cancer. Because of the poor prognosis associated with pancreatic cancer, some patients may try special diets with vitamin supplements, certain exercise programs, or unconventional treatments not yet approved by the FDA. Patients should always inform their doctors of any alternative treatments they are using as they could interfere with standard therapies. As of 2000, the National Cancer Institute (NCI) was funding phase III clinical trials of a controversial treatment for pancreatic cancer that involves the use of supplemental pancreatic enzymes (to digest cancerous cells) and coffee enemas (to stimulate the liver to detoxify the cancer). These theories remain unproven and the study is widely criticized in the medical community. It remains to been seen whether this method of treatment has any advantage over the standard chemotherapeutic regimen in prolonging patient survival or improving quality of life.

Coping with cancer treatment

Patients should discuss with their doctors any side effects they experience from treatment. Many drugs are available to relieve **nausea and vomiting** associated with cancer treatments and for combating fatigue. Special diets or supplements, including pancreatic enzymes, may be recommended if patients are experiencing digestive problems. Insulin or other medication may be prescribed if patients develop diabetes as a result of partial or total removal of their pancreas.

Clinical trials

A large number of clinical trials are underway to assess the therapeutic effect of new chemotherapy regimens and several new immunotherapies. Gemcitabine is being tested in combination with irinotecan (CPT-11) in patients with metastatic pancreatic disease. Other agents under investigation are DX-8951f and R115777. Some drugs are being tested in combination with radiation therapy or with biological therapies. Two preliminary studies using the vaccine G17DT showed a significant improvement in the survival of patients with advanced pancreatic

cancer. The monoclonal antibody cetuximab (IMC-C225) in combination with gemcitabine also showed positive preliminary results. There are trials available for patients with all stages of pancreatic cancer. Patients can find out which trials they are eligible for by talking with their doctors. Information about ongoing trials can be found at <http://cancernet.nci.nih.gov/trialsrch.shtml>. Many treatments given during clinical trials are considered experimental by **health insurance** companies and may not be covered by certain health plans. Patients should discuss their options with their doctors and health insurance providers.

Prevention

Although the exact cause of pancreatic cancer is not known, there are certain risk factors that may increase a person's chances of developing the disease. Quitting smoking will certainly reduce the risk for pancreatic cancer and many other cancers. The American Cancer Society recommends a diet rich in fruits, vegetables, and dietary fiber in order to reduce the risk of pancreatic cancer. According to the NCI, workers who are exposed to petroleum and other chemicals may be at greater risk for developing the disease and should follow their employer's safety precautions. People with a family history of pancreatic cancer are at greater risk than the general population, as a small percentage of pancreatic cancers are considered hereditary.

Special concerns

Pain control is probably the single greatest problem for patients with pancreatic cancer. As the cancer grows and spreads to other organs in the abdomen, it often presses on the surrounding network of nerves, which can cause considerable discomfort. In most cases, pain can be alleviated with analgesics or **opioids**. If medication is not enough, a doctor may inject alcohol into the abdominal nerve area to numb the pain. Surgical treatment of the affected nerves is also an option.

Pancreatic cancer patients frequently have difficulty maintaining their weight because food may not taste good or the pancreas is not releasing enough enzymes needed for digestion. Therefore, supplements of pancreatic enzymes may be helpful in restoring proper digestion. Other nutritional supplements may be given orally or intravenously in an effort to boost calorie intake. However, cachexia (severe muscle breakdown) caused by certain substances that the cancer produces, remains a significant problem to treat.

Patients with pancreatic cancer may experience anxiety and **depression** during their diagnosis and treatment. Statistics on the prognosis for the disease can be discouraging, however, there are many new treatments on the horizon that may significantly improve the outcome for this disease. Many patients find it helpful to join support groups where they can discuss their concerns with others who are also coping with the illness.

See also Cigarettes; Drug resistance; Gastrointestinal cancers; Immunologic therapies; Nutritional support; Pain management; Pancreatic cancer, endocrine; Smoking cessation.

KEY TERMS

Acinar cell(s)—Cells that comprise small sacs terminating the ducts of some exocrine glands.

Acinar cell carcinoma—A malignant tumor arising from the acinar cells of the pancreas.

Angiography—Diagnostic technique used to study blood vessels in a tumor.

Biopsy—Removal and microscopic examination of cells to determine whether they are cancerous.

Cancer vaccines—A treatment that uses the patient's immune system to attack cancer cells.

Chemotherapy— Drug treatment administered to kill cancerous cells.

Ductal adenocarcinoma—A malignant tumor arising from the duct cells within a gland.

Endoscopic retrograde cholangiopancreatography (ERCP)—Diagnostic technique used to obtain a biopsy. Also a surgical method of relieving biliary obstruction caused by a tumor.

Endoscopic ultrasonography (EUS)—Diagnostic imaging technique in which an ultrasound probe is inserted down a patient's throat to determine if a tumor is present.

Exocrine—Refers to glands which secrete their products through a duct.

Laparoscopic surgery—Minimally invasive surgery in which a camera and surgical instruments are inserted through a small incision.

Pancreatectomy—Partial or total surgical removal of the pancreas.

Radiation therapy—Use of radioisotopes to kill tumor cells. Applied externally through a beam of x rays, intraoperatively (during surgery), or deposited internally by implanting radioactive seeds in tumor tissue.

Whipple procedure—Surgical removal of the head of the pancreas, part of the small intestine, and some surrounding tissue.

QUESTIONS TO ASK THE DOCTOR

- What is my prognosis?
- What is the standard course of treatment for my cancer at this stage?
- How long will the course of treatment take?
- What side effects will I experience?
- What can be done to relieve my abdominal pain?
- What should I do to prepare for surgery?
- Can you refer me to a nutritionist or dietician?
- Are there any alternative therapies you would recommend?
- Am I eligible to participate in a clinical trial?
- Will my health insurance cover costs associated with a clinical trial?
- Are there any support groups I can join?

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Pap test

Definition

The Pap test is a procedure in which a physician scrapes cells from the cervix or vagina to check for **cervical cancer**, **vaginal cancer**, or abnormal changes that could lead to cancer. It often is called a Pap smear.

Purpose

The Pap test is used to detect abnormal growth of cervical cells at an early stage so that treatment can be started when the condition is easiest to treat. This microscopic analysis of cells can detect cervical cancer, precancerous changes, inflammation (vaginitis), infections, and some sexually transmitted diseases (STDs). The Pap test can occasionally detect endometrial (uterine) cancer or **ovarian cancer**, although it was not designed for this purpose.

Women should begin to have Pap tests at the age of 21 or within three years of becoming sexually active, whichever comes first. Young people are more likely to have multiple sex partners, which increases their risk of certain diseases that can cause cancer, such as human papillomavirus (HPV).

The American Cancer Society (ACS) updated its guidelines concerning Pap test frequency in late 2002. In brief, women should continue screening every year with

regular Pap tests until age 30, every two years if using the liquid-based Pap test. Once a woman age 30 and older has had three normal results in a row, she may get screened every two to three years. A doctor may suggest more frequent screening if a woman has certain risk factors for cervical cancer. Women who have had total hysterectomies including the removal of the cervix do not need Pap tests unless the hysterectomy resulted from cervical cancer. Those over age 70 who have had three normal results generally do not need to continue having Pap tests under the new guidelines.

Women with certain risk factors should always have yearly tests. Those at highest risk for cervical cancer are women who started having sex before age 18, those with many sex partners (especially if they did not use condoms, which protect against STDs), those who have had STDs such as genital herpes or genital warts, and those who smoke. Women older than 40 may have the test yearly, if experiencing bleeding after menopause. Women who have had a positive test result in the past may need screening every six months. Women who have had cervical cancer or precancer should have regular Pap smears.

Other women also benefit from the Pap test. Women over age 65 account for 25% of all cases of cervical cancer and 41% of deaths from this disease. Women over age 65 who have never had a Pap smear benefit the most from a Pap smear. Even a woman who has had a hysterectomy (removal of the uterus) should continue to have regular Pap tests at the discretion of the woman and the provider. If the surgery was for cancer, she may need to be examined more often than once a year. (Some women have the cervix left in place after hysterectomy.) Finally, a pregnant woman should have a Pap test as part of her first prenatal examination.

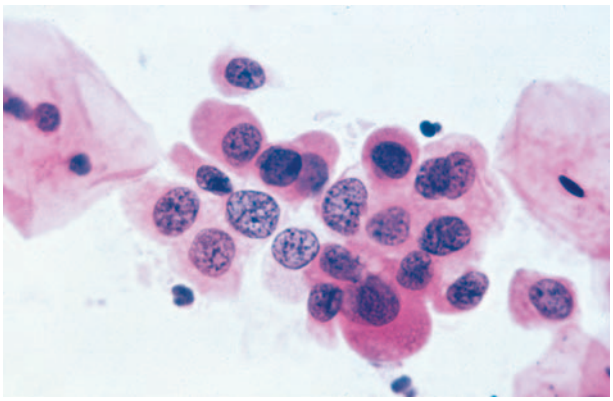
The Pap test is a **screening test**. It identifies women who are at increased risk of cervical dysplasia (abnormal cells) or cervical cancer. Only an examination of the cervix with a special lighted instrument (colposcopy) and samples of cervical tissue (biopsies) can actually diagnose these problems.

Precautions

The Pap test is usually not done during the menstrual period because of the presence of blood cells. The best time is in the middle of the menstrual cycle.

Description

The Pap test is an extremely cost-effective and beneficial test. Cervical cancer used to be a leading cause of cancer deaths in American women, but widespread use of this diagnostic procedure reduced the death rate from this disease by 74% between 1955 and 1992. A 2003 study reported that the test reduces rates of invasive cervical cancer by as much as 94%. In 2003, the FDA approved a new screening test that combines DNA testing for the HPV type that causes the most cases of cervical cancer with the standard Pap test, increasing its screening value.



These malignant cells were taken from a woman's cervix during a Pap test. *(Photograph by Parviz M. Pour, Photo Researchers, Inc. Reproduced by permission.)*

The Pap test, sometimes called a cervical smear, is the microscopic examination of cells scraped from both the outer cervix and the cervical canal. (The cervix is the opening between the vagina and the uterus, or womb.) It is called the "Pap" test after its developer, Dr. George N. Papanicolaou. This simple procedure is performed during a gynecologic examination and is usually covered by insurance. For those with coverage, Medicare will pay for one screening Pap smear every three years.

During the pelvic examination, an instrument called a speculum is inserted into the vagina to open it. The doctor then uses a tiny brush, or a cotton-tipped swab and a small spatula to wipe loose cells off the cervix and to scrape them from the inside of the cervix. The cells are transferred or "smeared" onto glass slides, the slides are treated to stabilize the cells, and the slides are sent to a laboratory for microscopic examination. The entire procedure is usually painless and takes five to ten minutes at most.

The newer method called liquid-based cytology, or the liquid-based Pap test, involves spreading the cells more evenly on a slide after removing them from the sample. The liquid-based method prevents cells from drying out and becoming distorted. Studies show that liquid-based testing slightly improves cancer detection and greatly improves detection of precancers, but it costs more than the traditional Pap test. Trade names in 2003 for liquid-based Pap smears were ThinPrep and AutoCyte.

Preparation

The Pap test may show abnormal results when a woman is healthy or normal results in women with cervical abnormalities as much as 25% of the time. It may even miss up to 5% of cervical cancers. Some simple preparations may help to ensure that the results are reliable. Among the measures that may help increase test reliability are:

- Avoiding sexual intercourse for two days before the test.
- Not using douches for two or three days before the test.
- Avoiding using tampons, vaginal creams, or birth control foams or jellies for two to three days before the test.
- Scheduling the Pap smear when not menstruating. However, most women are not routinely advised to make any special preparations for a Pap test.

If possible, women may want to ensure that their test is performed by an experienced gynecologist, physician, or provider and sent to a reputable laboratory. The physician should be confident in the accuracy of the chosen lab.

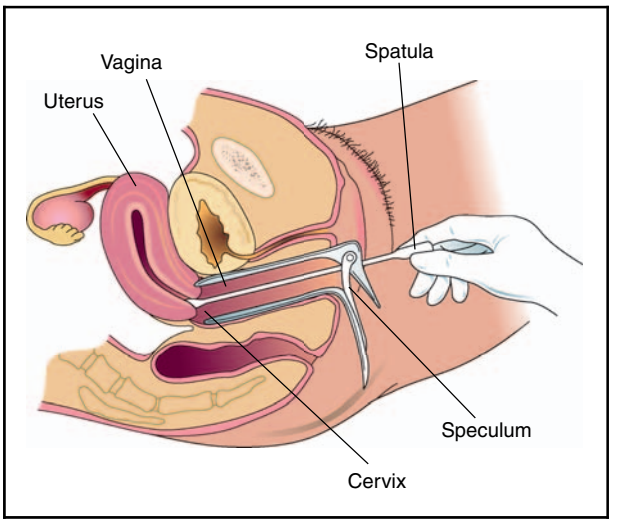
Before the exam, the physician will take a complete sexual history to determine a woman's risk status for cervical cancer. Questions may include date and results of the last Pap test, any history of abnormal Pap tests, date of last menstrual period and any irregularity, use of hormones and birth control, family history of gynecologic disorders, and any vaginal symptoms. These topics are relevant to the interpretation of the Pap test, especially if any abnormalities are detected. Immediately before the Pap test, the woman should empty her bladder to avoid discomfort during the procedure.

Aftercare

Harmless cervical bleeding is possible immediately after the test; a woman may need to use a sanitary napkin. She should also be sure to comply with her doctor's orders for follow-up visits.

Risks

No appreciable health risks are associated with the Pap test. However, abnormal results (whether valid or due to technical error) can cause significant anxiety. Women may wish to have their sample double-checked, either by the same laboratory or by the new technique of computer-assisted rescreening. The Food and Drug Administration (FDA) has approved the use of AutoPap and PAPNET to doublecheck samples that have been examined by technologists. AutoPap may also be used to perform initial screening of slides, which are then checked by a technologist. Any abnormal Pap test should be followed by colposcopy, not by double checking the Pap test.



The Pap test is a procedure used to detect abnormal growth of cervical cells that may be a precursor to cancer of the cervix. It is administered by a physician who inserts a speculum into the vagina to open and separate the vaginal walls. A spatula is then inserted to scrape cells from the cervix. These cells are transferred onto glass slides for laboratory analysis. The Pap test may also identify vaginitis, some sexually transmitted diseases, and cancers of the uterus and ovaries. *(Illustration by Electronic Illustrators Group. Reproduced by permission of The Gale Group.)*

Normal results

Normal (negative) results from the laboratory exam mean that no atypical, dysplastic, or cancer cells were detected, and the cervix is normal.

Abnormal results

Terminology

Abnormal cells found on the Pap test may be described using two different grading systems. Although this can be confusing, the systems are quite similar. The "Bethesda" system is based on the term "squamous intraepithelial lesion" (SIL). Precancerous cells are classified as "atypical squamous cells of undetermined significance," "low-grade" SIL, or "high-grade" SIL. Low-grade SIL includes mild dysplasia (abnormal cell growth) and abnormalities caused by HPV; high-grade SIL includes moderate or severe dysplasia and carcinoma in situ (cancer that has not spread beyond the cervix).

KEY TERMS

Carcinoma in situ—Malignant cells that are present only in the outer layer of the cervix.

Cervical intraepithelial neoplasia (CIN)—A term used to categorize degrees of dysplasia arising in the epithelium, or outer layer, of the cervix.

Dysplasia—Abnormal changes in cells.

Human papillomavirus (HPV)—The most common STD in the United States. Various types of HPV are known to cause cancer.

Neoplasia—Abnormal growth of cells, which may lead to a neoplasm, or tumor.

Squamous intraepithelial lesion (SIL)—A term used to categorize the severity of abnormal changes arising in the squamous, or outermost, layer of the cervix.

QUESTIONS TO ASK THE DOCTOR

- How will paracentesis benefit me?
- Will I have to have this procedure more than once?
- How soon after this procedure can I resume my normal activities?
- Will paracentesis cure my problem?
- Will I require hospitalization?

Another term that may be used is "cervical intraepithelial neoplasia" (CIN). In this classification system, mild dysplasia is called CIN I, moderate is CIN II, and severe dysplasia or carcinoma in situ is CIN III.

Regardless of terminology, it is important to remember that an abnormal (positive) result does not necessarily indicate cancer. Results may be falsely abnormal after infection or irritation of the cervix. Up to 40% of mild dysplasia reverts to normal tissue without treatment, and only 1% of mild abnormalities ever develop into cancer.

Treatment

CHANGES OF UNKNOWN CAUSE The most common abnormality found in Pap tests is atypical squamous cells of undetermined significance (ASCUS), which are found in 4% of all Pap tests. Sometimes these results are described further as either reactive or precancerous. Reactive changes suggest that the cervical cells are responding to inflammation, such as from a yeast infection. These women may be treated for infection and then undergo repeat Pap testing in three to six months. If those results are negative, no further treatment is necessary. This category may also include atypical "glandular" cells, which could imply a more severe type of cancer and requires repeat testing and further evaluation.

DYSPLASIA The next most common finding (in about 25 of every 1,000 tests) is low-grade SIL, which includes mild dysplasia or CIN I and changes caused by HPV. Unlike cancer cells, these cells do not invade normal tissues. Women are most susceptible to cervical dysplasia between the ages of 25 and 35. Typically, dysplasia causes no symptoms, although women may experience abnormal vaginal bleeding. Because dysplasia is precancerous, it should be treated if it is moderate or severe.

Treatment of dysplasia depends on the degree of abnormality. In women with no other risk factors for cervical cancer, mild precancerous changes may be simply observed over time with repeat testing, perhaps every four to six months. This strategy works only if women are diligent about keeping later appointments. Premalignant cells may remain that way without causing cancer for five to ten years, and may never become malignant.

In women with positive results or risk factors, the gynecologist must perform colposcopy and **biopsy**. A colposcope is an instrument that looks like binoculars, with a light and a magnifier, used to view the cervix. Biopsy, or removal of a small piece of abnormal, cervical or vaginal tissue for analysis, is usually done at the same time.

High-grade SIL (found in three of every 50 Pap tests) includes moderate to severe dysplasia or carcinoma in situ (CIN II or III). After confirmation by colposcopy and biopsy, it must be removed or destroyed to prevent further growth. Several outpatient techniques are available: conization (removal of a cone-shaped piece of tissue), laser surgery, **cryotherapy** (freezing), or the "loop electrosurgical excision procedure." Cure rates are nearly 100% after prompt and appropriate treatment of carcinoma in situ. Of course, frequent checkups are then necessary.

CANCER HPV, the most common STD in the United States, may be responsible for many cervical cancers. Cancer may be manifested by unusual vaginal bleeding or discharge, bowel and bladder problems, and pain. Women are at greatest risk of developing cervical cancer between the ages of 30 and 40 and between the ages of 50 and 60. Most new cancers are diagnosed in women between 50

and 55. Although the likelihood of developing this disease begins to level off for Caucasian women at the age of 45, it increases steadily for African-Americans for another 40 years. Biopsy is indicated when any abnormal growth is found on the cervix, even if the Pap test is negative.

Doctors have traditionally used **radiation therapy** and surgery to treat cervical cancer that has spread within the cervix or throughout the pelvis. In severe cases, post-operative radiation is administered to kill any remaining cancer cells, and **chemotherapy** may be used if cancer has spread to other organs. Recent studies have shown that giving chemotherapy and radiation at the same time improves a patient's chance of survival. The National Cancer Institute has urged physicians to strongly consider using both chemotherapy and radiation to treat patients with invasive cervical cancer. The survival rate at five years after treatment of early invasive cancer is 91%; rates are below 70% for more severe invasive cancer. That is why prevention, risk reduction, and frequent Pap tests are the best defense for a woman's gynecologic health.

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American College of Obstetricians and Gynecologists. 409 12th St. SW, PO Box 96920, Washington, DC 20090-6920. (202) 863-2518. <http://www.acog.com>.

National Cancer Institute, Office of Communications. 31 Center Dr., MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. <http://cancernet.nci.nih.gov/>.

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Paracentesis

Definition

Also known as peritoneal tap or abdominal tap, paracentesis consists of drawing fluid from the abdomen through a needle.

Purpose

Although little or no fluid is present in the abdominal (peritoneal) cavity of a healthy man, more than half an ounce may accumulate at certain times during a woman's menstrual cycle. Any cancer that originates in or spreads to the abdomen can result in fluid accumulation (malignant **ascites**).

Doctors remove fluid (ascites) from the abdomen to analyze its composition and determine its origin, to relieve the pressure and discomfort it causes, and to check for signs of internal bleeding This procedure should be performed whenever an individual experiences sudden or worsening abdominal swelling or when ascites is accompanied by **fever**, abdominal pain, confusion, or coma.

Paracentesis in cancer patients

When performed on a patient who has been diagnosed with cancer, paracentesis helps doctors determine the extent (stage) of the disease and whether conservative or radical treatment approaches would most effectively relieve symptoms or lengthen survival.

Precautions

Before undergoing paracentesis, a patient must make the doctor aware of any allergies, bleeding problems or use of anticoagulants, pregnancy, or possibility of pregnancy.

Description

Paracentesis is performed in a doctor's office or a hospital. The puncture site is cleansed and, if necessary,

shaved. The patient may feel some stinging as a local anesthetic is administered, and pressure as the doctor inserts a special needle (tap needle) into the abdomen. Occasionally, guidance with CT or ultrasound may be used.

When paracentesis is performed for diagnostic purposes, less than an ounce of fluid is drawn from the patient's abdomen into a syringe. As much as 15 ounces may be needed to determine whether ascites contains cancer cells. When the purpose of the procedure is to relieve pressure or other symptoms, many quarts of ascites may be drained from the abdomen. Because removing large amounts of fluid in a short time can cause dizziness, lightheadedness, and a sudden drop in blood pressure, the doctor may drain fluid slowly enough that the patient's circulatory system has time to adapt.

Laboratory analysis of abdominal fluid can detect blood, cancer cells, infection, and elevated protein levels often associated with malignant ascites. Results of these tests can help doctors determine the most appropriate course of treatment for a particular patient.

Preparation

No special preparations are required before this procedure. Patients should ask their doctors about special preparation requirements, but usually may eat, drink and take medications normally prior to paracentesis.

Aftercare

After removing the tap needle, the doctor may use a stitch or two to close any incision made (to ease the needle's entry into the abdomen) and applies an adhesive dressing to the puncture site.

Risks

Paracentesis occasionally causes infection. There is also a slight chance of the tap needle puncturing the bladder, bowel, or blood vessels in the abdomen. If large amounts of ascites are removed, the patient may need to be hospitalized and given intravenous (IV) fluids to prevent or correct severe fluid, protein, or electrolyte imbalances. A patient who has undergone extensive paracentesis should be warned about the possibility of fainting (syncope) episodes.

Normal results

Paracentesis is designed to establish the cause of, or to relieve symptoms associated with, an abnormal accumulation of fluid in the abdomen.

KEY TERMS

Appendicitis—Inflammation of the appendix.

Cirrhosis—Scarring of the liver (from infection or tumor) resulting in liver dysfunction

Lymphoma—Cancer of the lymph system.

Abnormal results

Laboratory tests of ascites may indicate the presence of:

- appendicitis
- cancer
- cirrhosis
- damaged bowel
- disease of the heart, kidneys, or pancreas
- infection

Ascites that contains cancer cells is usually bloody. Cloudy abdominal fluid has been found in patients with extensive intraabdominal lymphomas. Ascites will continue to accumulate until its cause is identified and eliminated. Some patients need to undergo paracentesis repeatedly.

Resources

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Maureen Haggerty

Paranasal sinus cancer

Definition

Paranasal sinus cancer is a disease in which cancer (malignant) cells are found in the tissues of the paranasal sinuses—the four hollow pockets of bone surrounding the nasal cavity.

Description

The paranasal sinuses, which are arranged symmetrically around the nasal cavity, include the:

- frontal sinuses (in the forehead, directly above the nose)
- ethmoidal sinuses (on each side of the nasal cavity, just behind the upper part of the nose)
- maxillary sinuses (on each side of the nasal cavity, in the upper region of the cheek bones)
- sphenoidal sinuses (behind the ethmoidal sinuses, in the center of the skull)

The paranasal sinuses, which normally contain air, are lined by mucous membranes that moisten the air entering the nose. Because they contain air, the sinuses allow the voice to echo and resonate.

Because the paranasal sinus area lies in an anatomically complex region, tumors in the paranasal sinuses can invade a variety of structures—such as the orbit (the bony cavity protecting the eyeball), the brain, the optic nerves, and the carotid arteries—even before symptoms appear.

The pharynx (throat) is divided into three sections: the nasopharynx, oropharynx, and laryngopharynx. The nasopharynx is the area behind (posterior to) the nose. The oropharynx is the area posterior to the mouth. The laryngopharynx opens into the larynx and esophagus. Usually, cancers of the paranasal sinuses originate in the lining of the nasopharynx or oropharynx. In rare cases, melanomas—a type of cancer arising from dark pigment-producing cells called melanocytes—may appear in the naso- or oropharynx. There is also an area of specialized sensory epithelium (surface layer of cells) through which the terminal branches of the olfactory nerve enter the roof of the nasal cavity, which gives rise to a very rare malignant neoplasm (growth) known as an esthesioneuroblastoma, or olfactory **neuroblastoma**.

Infrequently, a cancer may arise from the muscles or the soft tissues of the paranasal sinus region; these lesions are called **sarcomas**. Occasionally, lesions called midline granulomas (a granular-type tumor usually from lymphoid or epithelioid cells) occur; these lesions arise in the nose or paranasal sinuses and spread to surrounding tissues. Also rare are slow-growing cancers called inverting papillomas (papillae are tiny, nipple-like protuberances).

Demographics

Malignant growths of the paranasal sinuses are uncommon in the general population. Paranasal sinus cancer represents 3% of all cancers in the upper aerodigestive tract (air and food passages) and less than 1% of all malignancies in the body. The incidence of paranasal sinus cancer is about one case per 100,000 people per year in the United States. Only about 200 new cases a year are diagnosed in the United States. The disease is more common in Asia Minor and China than in Western countries. The incidence of maxillary sinus cancer is highest in the South African Bantus and in Japan.

Paranasal sinus tumors occur about two to three times more frequently in men than women, and diagnosis usually occurs between the ages of 50 and 70. Cancers of the maxillary sinus are the most common of the paranasal sinus cancers, occurring in about 80% of individuals. Tumors of the ethmoidal sinuses are less common (about 20%), and tumors of the sphenoidal and frontal sinuses are rarest (less than 1%).

Squamous cell carcinoma (cancer that originates from squamous keratinocytes in the epidermis, the top layer of the skin) is the most frequent type of malignant tumor in the paranasal sinuses (about 80%). **Adenocarcinomas** (cancer that begins in cells that line certain internal organs and that have glandular, or secretory, properties) constitute 15%, and the remaining 5% are composed of all other types.

Causes and symptoms

Although the causes of paranasal sinus cancer are not known, several occupational groups have been found to have an increased risk of developing these tumors. These groups include leather and textile workers, nickel refiners, woodworkers, and manufacturers of isopropyl alcohol, chromium, and radium. Also, snuff and thorium dioxide (a radiological contrast agent) have been associated with an increased incidence of paranasal sinus cancer. It is unclear whether these factors cause cancer by direct **carcinogenesis** (cancer production) or by altering the normal nasal epithelial physiology.

Nickel workers primarily develop squamous cell carcinomas, which usually arise in the nasal cavity. Woodworkers, however, usually develop adenocarcinomas that usually arise in the ethmoidal sinuses. The incidence of adenocarinomas in these workers is 1,000 times higher than that of the general population. Tobacco and alcohol use have not been demonstrated conclusively as a causative factor in the development of paranasal sinus tumors. However, viral agents, especially the **human papilloma virus** (HPV), may also play a causative role.

In patients with cancer of the head and neck, the immune system is often not functioning properly. Malignant cells are not recognized as foreign, or when recognized, the immune system does not effectively destroy

cancer cells. Causes of the failure of the immune system include severe malnutrition, substances in the tumor that deactivate the immune system, or a genetic predisposition.

The symptoms of paranasal sinus cancer vary with the type, location, and stage of cancer present. Symptoms typical of early lesions often resemble those of an upper respiratory tract infection and include nasal obstruction, facial pain, and thin, watery nasal discharge (rhinorrhea), which can at times be blood-tinged. The key factor that differentiates the symptoms of an upper respiratory infection from a malignant lesion, however, is the duration of the symptoms. An upper respiratory infection generally clears up or improves dramatically in several weeks with appropriate medical care, but symptoms associated with a malignancy persist.

The most common symptoms of paranasal sinus cancer include:

- persistently blocked nose
- feeling of recurrent "sinus infections"
- bleeding without apparent cause from the nose or the paranasal sinuses
- progressive pain and swelling of the upper region of the face or around the eyes
- closing up of one eye, blurred vision, or visual loss
- persistent pain in the forehead, the front of the skull, or over the cheekbones
- swelling in the roof of the mouth
- loosening of teeth, poorly fitting dentures, or bleeding from upper teeth sockets

Tumors in the nasal cavity and paranasal sinuses metastasize (spread) to the cervical lymph nodes (lymph nodes in the neck) in about 15% of individuals.

Diagnosis

There are several steps in establishing a diagnosis of paranasal sinus cancer. The first step is a thorough medical history, followed by a physical examination. The physical examination may reveal a lesion in the nose or a submucosal (below the mucous membrane) mass arising in an adjacent sinus.

After the history and physical examination, a series of tests are performed to determine the precise nature of the suspicious growth and the extent of its spread. These tests may include:

- **Biopsy** (the removal of a sample of tissue that appears to be suspicious) is performed after a lesion is identified. The tissue is studied under the pathologist's microscope.
- **Computed tomography** (CT) scan, which is a series of detailed pictures with thin cross-sectional slices taken radiologically through the body and interpreted with a computer.
- Nasoscopy, which utilizes an instrument called the nasoscope for examining the nasal cavity and the paranasal sinuses.
- **Magnetic resonance imaging** study (MRI), an imaging study that consists of detailed pictures, but instead of using x rays, a powerful magnet is used to polarize electrons inside the body to obtain images, which are then interpreted by a computer.
- Posterior rhinoscopy, in which the nasopharynx and the rear portion of the nose are examined using a light and a special mirror.

Although endoscopic techniques (visualizing the nasal cavity with an endoscope—a tube-like device to which an optical system is attached) have greatly improved the ability to examine the nasal cavities and the paranasal sinuses, radiographic studies are also necessary in completing the evaluation. The most important radiographic studies include CT and MRI scans, usually used in combination. The MRI scan has become the most essential radiographic test for accurate delineation of pretreatment tumor extent, and also for following up patients after treatment.

However, each scanning technique has its own advantages and limitations. The CT scan is preferred in evaluating the bony structures in the paranasal sinus area. The MRI better assesses soft-tissue differences, enabling not only the differentiation of tumor from inflammatory changes in the nose and sinuses, but also the determination of involvement of the soft tissues in, for example, the orbit, the brain, and the optic nerve.

Obtaining a biopsy is crucial to diagnosis. Endoscopic sinus surgery is widely used for obtaining tissue for biopsy. Combining endoscopic surgery with CT imaging, however, allows the surgeon access into small recesses of the nose and sinuses and along the base of the skull, making biopsy not only more accurate but also safer for the patient.

Treatment team

Patients with paranasal sinus cancer are usually treated by a team of specialists using a multifaceted approach. Each patient receives a treatment plan that is tailored to fit his or her requirements, specifically the patient's overall constitution, grade, and stage of disease. Usually, however, the treatment team includes:

- an otorhinolaryngologist (ear, nose, and throat specialist)

- an oncologist (cancer specialist)
- a radiotherapist (x-ray treatment specialist)

If extensive surgery is required, a plastic and reconstructive surgeon may also serve as part of the treatment team.

Clinical staging, treatments, and prognosis

Paranasal sinus cancer staging involves carefully establishing the degree of cancer spread. If the cancer has spread, it is also necessary to establish the extent of spread and organ involvement.

Cancer grading is a microscopic issue; the pathologist determines the degree of aggressiveness of the cancer. The term well-differentiated means less aggressive; the terms moderately differentiated, intermediately aggressive, and poorly differentiated mean more aggressive.

Both grading and staging help the physician establish the prognosis (degree of seriousness of the disease) and likely outcome.

Staging

Staging may involve additional imaging tests such as CT scan of the brain, abdominal ultrasound, bone scan, or chest **x ray**. Although no clear-cut staging protocol exists for the relatively uncommon cancers of the paranasal sinuses, the following practical staging exists for cancer of the maxillary sinuses, the most common cancer of this area:

- Stage I: The cancer is confined to the maxillary sinus, with no bony erosion or spread to the lymph nodes.
- Stage II: The cancer has begun to destroy the surrounding bones but without spread to the lymph nodes.
- Stage III: The cancer has spread no farther than the bones around the sinus and to one node on the same side of the neck, and is no greater than 3 cm (1.1 in) in size, or has spread to the cheek, the rear portion of the sinus, the eye socket, or the ethmoidal sinus (spread to lymph nodes on the same side of the neck may or may not be present).
- Stage IV: The cancer has spread to the eye, other sinuses, or tissues adjacent to the sinuses (spread to lymph nodes on the same side of the neck may or may not be present). The cancer may have spread within the sinus itself or to surrounding tissues, to lymph nodes in the neck on one or both sides, to any node larger than 6 cm (2.3 in), or to other parts of the body. Recurrent maxillary sinus cancer—either in the same location or in a different one after primary treatment has been completed—is also in this category.

Treatment options

The major treatment options for paranasal sinus cancer include:

- Surgery. May be necessary for the removal of a section of the nasal cavity or the paranasal sinus at any stage of the disease. Also, some **lymph node dissection** may be required in the neck, depending upon the staging and grading. May be combined with radiotherapy at any stage, depending on the type of cancer and its location.
- Radiotherapy. Also called **radiation therapy**, radiotherapy is sometimes used alone in stage I and II disease, or in combination with surgery in any stage of the disease. In the early stages of paranasal sinus cancer, radiotherapy is considered the alternative local therapy to surgery. Radiotherapy involves the use of high energy, penetrative rays to destroy cancer cells in the zone treated. Radiation therapy is also employed for palliation (control of symptoms) in patients with advanced cancer. Teletherapy (external radiation) is administered via a machine remote from the body while internal radiation (brachytherapy) is given by implanting a radioactive source into the cancerous tissues. Patients may or may not require both types of radiation. Radiotherapy usually takes just five to ten minutes per day, five days a week for about six weeks, depending upon the type of radiation used.
- **Chemotherapy**. Usually reserved for stage III and IV disease. Besides local therapy, the best attempt to control cancer cells circulating in the body is by using systemic therapy (therapy that affects the entire body) in the form of injections or oral medications. This form of treatment, called chemotherapy, is given in cycles (each drug or combination of drugs is usually administered every three to four weeks). Chemotherapy may also be used in combination with surgery, radiotherapy, or both.

At the forefront of research into head and neck cancer, molecular biology and gene therapy are providing new insights into the basic mechanisms of cancer genesis and treatment. The detection of various oncogenes (genes that can induce tumor formation) in head and neck cancer is also progressing rapidly. Gene therapy trials, still in their infancy as of 2005, are also introducing genetic material to help the immune system recognize cancer cells.

Alternative and complementary therapies

Alternative and complementary therapies may also be used at any stage of the disease. Alternative treatments are treatments used instead of conventional treatments. Complementary therapies are used in addition to

conventional treatments. Although not specifically used in treating paranasal sinus cancer, there is much anecdotal (nonscientific) evidence for a number of alternative cancer therapies. Some insurance plans cover complementary therapies, such as acupuncture.

The safest and most accepted of these complementary therapies include:

- acupuncture
- biofeedback
- diet that includes fresh fruit, vegetables, and whole grains
- massage
- meditation, prayer, or creative visualization
- vitamins (especially **antioxidants** A, E, and C), minerals, and herbs

The National Center for Alternative and Complementary and Alternative Medicine, part of the National Institutes of Health, discusses some alternative and complementary cancer treatments on its web site <http://www.nccam.nih.gov>.

Prognosis

The high mortality rate and poor prognosis association with paranasal sinus cancer is related to late diagnosis. Most lesions (75%) are at an advanced stage at the time of definitive diagnosis. Surgical treatment alone may be sufficient for stage I or II lesions if adequate surgical margins are obtained. However, for advanced tumors, combined therapy with radical surgical excision and postoperative radiotherapy has been demonstrated to improve the five-year survival rate.

The primary cause of death is failure of local control. Most paranasal sinus cancers grow rapidly and invade nearby tissues but are slow to spread to distant sites. Thus, patients with advanced disease usually die from a local recurrence of the tumor, even after aggressive treatment.

Coping with cancer treatment

Cancer treatments such as radiotherapy and chemotherapy not only destroy cancer cells but also damage healthy tissue. The effects of radiation depend upon the dose of radiation, the size of the area radiated, and the number and size of each fraction. When doses are fractionated, the total dose of radiation therapy is divided into several smaller, equal doses delivered over a period of several days.

The most common side effect of radiotherapy is extreme **fatigue**. Although rest is encouraged, most radiotherapists advise patients to move around as much as possible. Another common side effect is radiation dermatitis—the skin covering the radiated area becomes red, dry, itchy, and may show signs of scaling. This skin problem is associated only with teletherapy (external radiation therapy).

Radiation also may cause **nausea and vomiting**, **diarrhea**, and urinary discomfort. There may also be a decrease in white blood cells, which are needed to fight infection. Usually the radiotherapist can suggest the drugs and diet necessary to alleviate these problems.

Chemotherapy drugs may cause a wide spectrum of side effects. The severity of these symptoms vary with

KEY TERMS

Adenopathy—Large or swollen lymph glands.

Adjuvant therapy—Treatment (such as chemotherapy, radiation therapy, or hormone therapy) given after the primary treatment to increase the chances of a cure.

Adenocarcinoma—Cancer that begins in cells that line certain internal organs and that have glandular (secretory) properties.

Angiogenesis inhibitor—A substance that prevents the growth of new blood vessels.

Antimetabolite—A chemical very similar to one required in normal biochemical reactions in cells; an antimetabolite can stop or slow down the reaction.

Antineoplaston—A substance isolated from normal human blood and urine and tested as a type of treatment for some tumors and AIDS. Treatment is considered experimental in 2001.

Epithelium—A thin layer of tissue that covers organs, glands, and other structures within the body.

Monoclonal antibody—Laboratory-produced substance that can locate and bind to cancer cells.

Nasal cavity—The cavity between the floor of the cranium and the roof of the mouth.

Neoplasm—Any new and abnormal formation of tissue, as a tumor or growth.

Radiotherapy—Radiation treatment (external or internal).

each drug and with each individual. Some of the most common side effects of chemotherapy include:

- diarrhea
- hair loss (**alopecia**)
- hearing loss
- skin rashes
- tingling and numbness in the fingers and toes
- vomiting

Most of these side effects are treatable, temporary, and recede after therapy ends. However, the attitude of the patient is very important during cancer therapy. The better psychologically prepared the patient is for treatment, the better the chances of experiencing decreased side effects.

QUESTIONS TO ASK THE DOCTOR

- What kinds of treatments will I receive?
- What benefits can be expected from this therapy?
- What are the risks and side effects of these treatments?
- Will my treatments be covered by health insurance?
- What clinical trials are available for this type of cancer? Am I a candidate?
- Are there any complementary treatments that would benefit me?

If extensive surgery is required, reconstruction and rehabilitation by specialized physicians can improve the patient's quality of life.

Clinical trials

As of 2005, 35 **clinical trials** involving paranasal sinus cancer were operating in the United States. Clinical trials can be located at the web site <http://www.clinicaltrials.gov>, a service of the National Institutes of Health and the National Library of Medicine.

Some of the new drugs under investigation for advanced, recurrent, or metastatic head and neck cancer—either alone, in combination, with concurrent radiotherapy, or with standard chemotherapy drugs such as **fluorouracil** (5-FU), **paclitaxel**, or **cisplatin**—include:

- A10 and AS2-1 (antineoplastons)
- Dimesna (chemoprotective agent)
- Fenretinide (retinoid, or vitamin A derivative)
- **Filgrastim** (G-CSF or granulocyte colony-stimulating factor; increases white blood cells)
- Flavopiridol (cyclin-dependent kinase [Cdk] inhibitor; kinases plays a role in cell cycle regulation and tumor formation)
- Gemcitabine (antimetabolite)
- ONYX-015 (genetically engineered cold virus)
- C225/cetuximab (monoclonal antibody)
- Oxaliplatin (platinum compound; chemotherapeutic agent)
- SU5416 (angiogenesis inhibitor)

Prevention

The causes of paranasal sinus cancer are unknown. However, avoiding environmental risk factors such as heavy smoking or drinking, or inhaling wood dust or other toxic substances (such as isopropyl alcohol, chromium, or radium) on a regular basis may decrease the chances of developing this form of cancer.

Special concerns

Although surgical treatment of squamous cell carcinoma of the head and neck offers the best chance for cure in many patients, the results of the surgery have often been extremely disfiguring and functionally debilitating. The changes in facial appearance and loss of ability to speak, swallow, and breathe normally can be devastating, both physically and psychologically.

If the anticipated surgical defect is large, often a reconstructive team will harvest tissue from a distant site in the body to use as a graft while the oncology team is removing the cancer. Initially, reconstructive teams were more concerned with simply closing the surgical defect and re-establishing a more natural form. Increasingly, the focus has been to re-establish normal function.

Resources

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ORGANIZATIONS

American Cancer Society, 1599 Clifton Road, NE, Atlanta, GA 30329-4251. <http://www.cancer.org>. Phone: 1-800-ACS-2345.

National Cancer Institute. Public Inquiries Office, Building 31, Room 10A03, 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. <http://www.nci.nih.gov>. Phone: 1-800-4-CANCER.

National Center for Complementary and Alternative Medicine (NCCAM), NCCAM Clearinghouse, P.O. Box 8218, Silver Springs, MD 20907-8218. <http://www.nccam.nih.gov>. Phone: 1-888-644-6226.

OTHER

Cancernet (List of organizations and web sites offering information and services for cancer patients and their families). <http://www.cancernet.nci,nih.gov/cancerlinks.html>.

<cancersource.com> (Cancer resources for patients and families).

<http://www.clinicaltrials.gov>. (List of clinical trials).

Genevieve Slomski, Ph.D.

Paraneoplastic syndromes

Description

Paraneoplastic syndromes are rare disorders caused by substances that are secreted by a benign tumor, a malignant (cancerous) tumor, or a malignant tumor's metastases. The disturbances caused by paraneoplastic syndromes occur in body organs at sites that are distant or remote from the primary or metastatic tumors. Body systems that may be affected by paraneoplastic syndromes include neurological, endocrine, cutaneous, renal, hematologic, gastrointestinal, and other systems. The most common manifestations of paraneoplastic syndromes are cutaneous, neurologic, and endocrine disorders. An example of a cutaneous paraneoplastic disorder are telangiectasias, which can be caused by **breast cancer** and lymphomas. Lambert-Eaton myasthenic syndrome (LEMS, and also known as Eaton-Lambert syndrome) is a neurologic paraneoplastic syndrome that can be caused by a variety of tumors including small cell lung cancer, **lymphoma**, breast, colon and other cancers. **Syndrome of inappropriate antidiuretic hormone** (SIADH) is an endocrine paraneoplastic syndrome, which is seen in as many as 40% of patients diagnosed with small cell lung cancer.

Approximately 15% of patients already have a paraneoplastic disorder at the time of initial diagnosis with cancer. As many as 50% of all cancer patients will develop a paraneoplastic syndrome at some time during the course of their disease. Some clinicians categorize the **anorexia**, cachexia, and **fever** which occur as a result of cancer as metabolic paraneoplastic syndromes. Virtually all patients diagnosed with cancer are affected by at least one of these metabolic paraneoplastic syndromes.

Paraneoplastic syndromes can occur with any type of malignancy. However, they occur most frequently with lung cancer, specifically small-cell lung **carcinoma**. Other types of cancer that commonly cause paraneoplastic syndromes are breast cancer and stomach cancer. With the exception of **Wilms' tumor** and **neuroblastoma**, paraneoplastic syndromes do not usually occur in children diagnosed with cancer.

In general, paraneoplastic syndromes may be present in the patient before a diagnosis of cancer is made, or, as stated earlier, may be present at the time the patient is first diagnosed with cancer. Most paraneoplastic syndromes appear in the later stages of the disease. Frequently, the presence of a paraneoplastic syndrome is associated with a poor prognosis. Paraneoplastic syndromes are difficult to diagnose and are often misdiagnosed. Some paraneoplastic syndromes may be confused with metatastic disease or spread of the cancer. The presence of the syndrome may be the only indication that a patient has a malignancy or that a malignancy has recurred. Paraneoplastic syndromes may be useful as clinical indicators to evaluate the response of the primary cancer to the treatment. Resolution of the paraneoplastic syndrome can be correlated with tumor response to treatment. That is, if the paraneoplastic syndrome resolves, the tumor has usually responded to the treatment.

KEY TERMS

Anorexia—Loss of appetite.

Cachexia—Severe malnutrition, emaciation, muscle wasting and debility associated with the inability to absorb the nutritional value of food eaten.

Cutaneous disorders—Disorders affecting the skin.

Hypokalemia—Decreased levels of the electrolyte potassium in the blood.

Hyponatremia—Decreased levels of the electrolyte sodium in the blood.

Metastasis—Tumors which originate from the primary or original tumor at distant locations in the body; secondary tumors.

Neurologic disorders—Disorders affecting the nervous system.

Causes

Paraneoplastic syndromes occur when the primary or original tumor secretes substances such as hormones, proteins, growth factors, cytokines, and antibodies. The substances are referred to as mediators. These mediators have effects at remote or distant body organs, which are termed target organs. Mediators interfere with communication between cells in the body. This miscommunication results in abnormal or increased activity of the cell's normal function. For example, a lung tumor may cause the paraneoplastic syndrome, ectopic **Cushing's syndrome**, which is the result of abnormal functioning of the pituitary gland located in the brain. In this example, the lung cancer is the primary tumor and the pituitary gland is the target organ. Ectopic Cushing's Syndrome is caused by overproduction of the mediator, adrenocorticotropic hormone (ACTH).

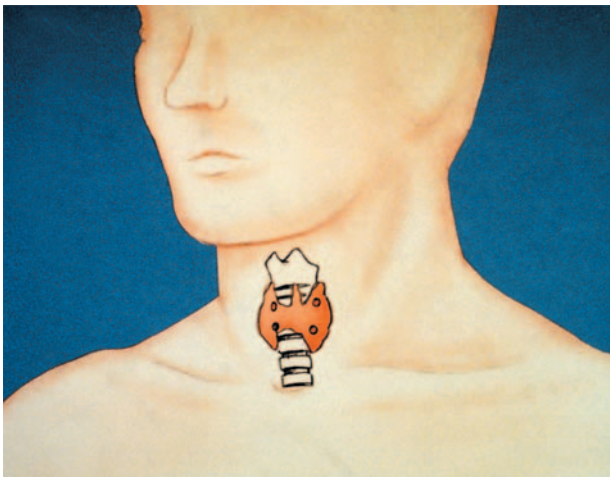
Treatment

There are usually two approaches taken in the treatment of paraneoplastic syndromes. The first step is treatment of the cancer that is causing the syndrome. This treatment can be surgery, administration of **chemotherapy**, biotherapy, **radiation therapy**, or a combination of these therapies. The next approach is to suppress the substance or mediator causing the paraneoplastic syndrome. Often treatment targeted to the underlying cancer and to the paraneoplastic syndrome occur at the same time. However, even with treatment, irreversible damage to the target organ can occur.

Selected Paraneoplastic Syndromes

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH) SIADH is a common paraneoplastic syndrome that affects the endocrine system. This syndrome is most often associated with small cell lung cancer; however, other cancers such as brain tumors, leukemia, lymphoma, colon, prostate, and **head and neck cancers** can lead to SIADH. SIADH is caused by the inappropriate production and secretion of arginine vasopressin or antidiuretic hormone (ADH) by tumor cells. Patients with SIADH may not have symptoms, especially in the early stages. When symptoms do occur they are usually related to hyponatremia, which leads to central nervous system toxicity if left untreated. Signs and symptoms associated with hyponatremia include **fatigue**, anorexia, headache and mild alteration in mental status in early stages. If SIADH remains untreated, symptoms can progress to confusion, delirium, seizures, coma, and death. Treatment approaches for SIADH are to treat the underlying tumor and restriction of fluids. More severe cases may require the administration of medications.

LAMBERT-EATON MYASTHENIC SYNDROME Lambert-Eaton myasthenic syndrome, also known as LEMS and Eaton-Lambert syndrome, has been associated with a



The parathyroid glands, embedded in the thyroid gland but separate from the thyroid in function, control calcium metabolism in the body by producing parathyroid hormone (PTH). Cancer of the parathyroid glands is rare. *(Photograph by Rick Hall. Custom Medical Stock Photo. Reproduced by permission.)*

number of cancers including small-cell lung cancer, lymphoma, breast, stomach, colon, and prostate cancers. Potential mediators associated with paraneoplastic LEMS are antibodies that interfere with release of acetylcholine at the neuromuscular junction. This interference prevents the flow of calcium, which results in decreased or absent impulse transmission to muscle. The disruption in muscular impulse transmission leads to mild symptoms including weakness in the legs and thighs, muscle aches, muscle stiffness, and muscle fatigue. Treatment of LEMS includes administration of **corticosteroids**, intravenous immunoglobulin, and plasmapheresis. Depending on the extent of damage, irreversible loss of function may occur even with treatment.

ECTOPIC CUSHING'S SYNDROME Cushing's Syndrome is most often associated with small cell lung cancer, **ovarian cancer**, and medullary cancers of the thyroid. ACTH precursors are activated by tumor cells that results in overproduction of ACTH by the pituitary gland. Signs and symptoms of ectopic Cushing's Syndrome include hypertension, hyperglycemia, hypokalemia, edema, muscle weakness, and **weight loss**. The primary approach to treating ectopic Cushing's Syndrome is to treat the underlying cancer. In early stages, surgery is the treatment of choice. However, surgery is not usually an option for patients diagnosed with small cell cancer of the lung. If the tumor is unable to be removed or controlled, or if the patient has severe symptoms, then treatment targeted to the syndrome is initiated. Medical therapy is usually focused on inhibiting cortisol production and involves the use of medications such as ketoconazole and **aminoglutethimide**.

Resources

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Melinda Granger Oberleitner, R.N., D.N.S.

Parathyroid cancer

Definition

Parathyroid cancer is a rare, slow-growing tumor of a parathyroid gland in the neck.

Description

The four parathyroid glands in the human body are designated as the right superior, right inferior, left superior, and left inferior glands. They usually lay adjacent to the thyroid, but rarely can be found in the upper chest. The parathyroid glands secrete parathyroid hormone, which plays a central role in regulating calcium levels in the blood. In the condition called primary hyperparathyroidism, excess production of parathyroid hormone leads to abnormally high levels of calcium (**hypercalcemia**). Adenomas, or hyperplasia, of the parathyroid glands are responsible for about 99% of all cases of primary hyperparathyroidism. Parathyroid cancer accounts for the remaining 1%.

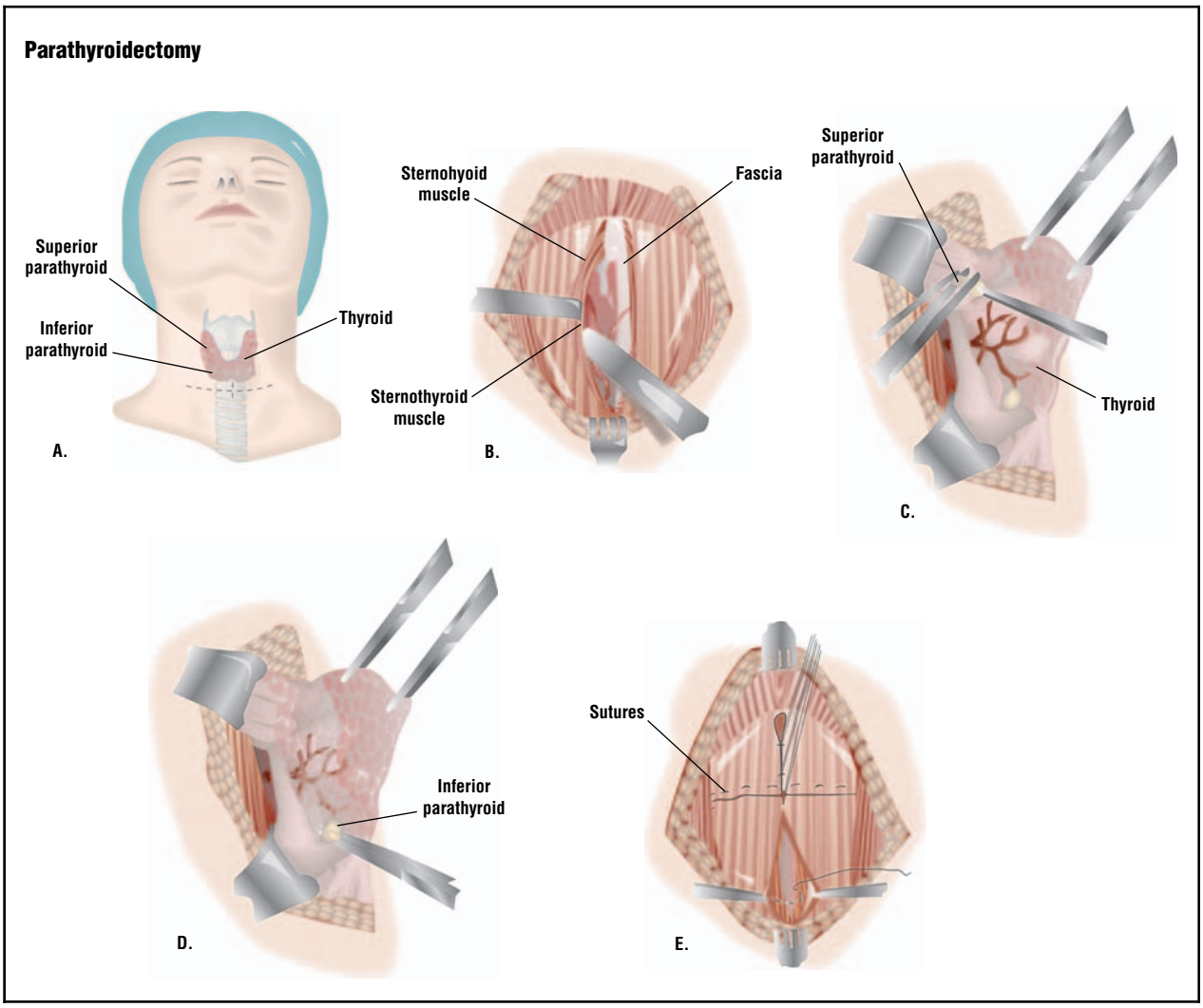
Parathyroid cancer is a slow-growing tumor that manifests itself mainly by production of parathyroid hormone.

Demographics

Only a few hundred cases of parathyroid cancer have been reported in medical literature. It is more common in Japan than in Western countries. No gender preference has been reported. The average age of the patient with parathyroid cancer is in the fifth decade.

Causes and symptoms

Unlike some cancers, there are no predisposing factors that have been found to clearly increase the risk for



(Illustration by Argosy Publishing. Reproduced by permission of The Gale Group.)

parathyroid cancer. There are some reported cases of parathyroid cancer arising in patients with adenomas or hyperplasia of the parathyroid.

Most parathyroid cancers are functioning tumors, in that they overproduce parathyroid hormone. Thus, the signs and symptoms of parathyroid cancer are chiefly related to hyperparathyroidism and the resultant hypercalcemia. Common complaints are weakness, **fatigue**, **weight loss**, **anorexia**, constipation, nausea, and vomiting. Patients may also report frequent urination and extreme thirst. Since excess parathyroid hormone causes bones to release too much calcium into the bloodstream, patients may experience **bone pain** and fractures. The extra calcium in the blood can be deposited in the kidneys, leading to the formation of painful kidney stones. Pancreatitis is another consequence of hypercalcemia. The levels of parathyroid hormone and calcium in patients with parathyroid cancer are usually dramatically elevated—much more so than in patients with benign causes of hyperparathyroidism.

Sometimes the parathyroid cancer is large enough to form a mass in the neck that can be easily felt. If the mass is large enough, it can impinge upon a nerve that controls the vocal cords, leading to hoarseness. In contrast, these features are uncommon in benign hyperparathyroidism.

Diagnosis

The diagnosis of parathyroid cancer can be difficult because it produces symptoms similar to those of benign hyperparathyroidism due to adenomas or hyperplasia. However, the symptoms of parathyroid cancer are generally more severe and the levels of parathyroid hormone

KEY TERMS

Adenoma—Benign tumor derived from glandular structures.

Biopsy—Obtaining a piece of tissue from a living being for diagnostic examination.

Computed tomography—A radiology test by which images of cross-sectional planes of the body are obtained.

Diuretic—A drug that promotes the excretion of urine.

Hyperplasia—Generalized overgrowth of a tissue or organ due to excess number of cells.

Magnetic resonance imaging—A radiology test that reconstructs images of the body based on magnetic fields.

Pancreatitis—Inflammation of the pancreas.

Peptic ulcer—Distinct erosions of the inner layer of the stomach or small intestine.

Scintigraphy—A radiology test that involves injection and detection of radioactive substances to create images of body parts.

Ultrasound—A radiology test utilizing high-frequency sound waves.

and calcium are usually higher. The presence of a neck mass or hoarseness also suggests cancer. Beyond this, there are no biochemical or radiological tests that can definitively diagnose parathyroid cancer.

There are four general scenarios for the diagnosis of parathyroid cancer:

- Parathyroid cancer is suspected, based on symptoms and signs. Surgery is performed with the intent to remove the cancer.
- A patient with hyperparathyroidism undergoes surgery to remove one or more glands that are thought to contain an **adenoma** or hyperplasia. During surgery, it is discovered that the underlying lesion is most likely cancer.
- Similarly, a patient with hyperparathyroidism undergoes surgery to remove one or more glands that are thought to contain an adenoma or hyperplasia. After the surgery is complete, the resected specimen is found to contain cancer.
- When symptoms of hyperparathyroidism reappear after surgery, it should raise the suspicion of an incompletely treated parathyroid cancer. This cancer may be localized to the neck or may have spread to distant organs. Several imaging tests can be helpful in this situation. Scintigraphy and ultrasound are useful in detecting recurrent tumors in the neck. **Computed tomography** (CT scan) and **magnetic resonance imaging** (MRI) can detect cancer at distant organs, such as the lungs or liver. Sometimes, careful **biopsy** of a suspected tumor may confirm the diagnosis of cancer.

Clinical staging, treatments, and prognosis

Parathyroid cancer begins in the parathyroid gland and extends to adjacent structures. Late in the course of the disease, it spreads to lymph nodes and ultimately to the lungs and liver.

The best treatment for parathyroid cancer is surgical removal of the cancerous gland. In order to assure complete resection of the cancer, part of the thyroid gland, nearby lymph nodes, and other adherent tissue must be removed with the specimen. Cancer that has spread to distant organs should be removed if possible.

Surgical cure is not possible if the cancer has spread too widely. Therapy then becomes focused on controlling hypercalcemia. General measures include infusing saline solution intravenously to restore lost fluid and to encourage urinary excretion of calcium. Diuretics are drugs that further stimulate urinary excretion of calcium. Bisphosphonates and plicamycin both inhibit the release of calcium from the bone. Other agents, such as **gallium nitrate**, have shown promise in the treatment of hypercalcemia associated with parathyroid cancer. However, further studies must be conducted to confirm their effectiveness and safety.

The prognosis of parathyroid cancer depends upon the stage of the cancer and the completeness of the surgical resection. If the cancer is detected early and completely removed, cure is possible, but the cancer has been reported to recur up to 20 years after surgery. Cure is unlikely after recurrence. Even so, survival can be signficantly extended by surgery aimed at removing as much recurrent or distant cancer as possible. In general, parathyroid cancer grows and spreads slowly, so that oversecretion of parathyroid hormone is more clinically evident than the actual growth of the cancer.

Alternative and complementary therapies

There have been a few cases in which **radiation therapy** or **chemotherapy** have been reported to partially control the growth and symptoms of parathyroid cancer. In the majority of patients, these interventions have not been successful.

Resources

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Kevin O. Hwang, M.D.

PC-SPES

Definition

PC-SPES is an herbal mixture of eight botanical compounds adapted from traditional Chinese medicine that is used to treat **prostate cancer**, particularly the forms that do not respond to anti-androgen (hormone) therapy.

As PC-SPES is considered an alternative treatment for cancer, the National Center for Complementary and Alternative Medicine (NCCAM) began to conduct four separate clinical trials of the compound in the early 2000s. These studies were put on hold in June 2002, after the Food and Drug Administration (FDA) determined that samples of PC-SPES were contaminated with "undeclared prescription drug ingredients that could cause serious health effects if not taken under medical supervision." The California distributors of the product voluntarily recalled it, and closed their business at the end of 2002.

Because the early trials of PC-SPES gave promising results, NCCAM is interested in funding newer studies of the product, but will not do so until a fully standardized and uncontaminated product using the original formulation becomes available.

Purpose

PC-SPES is an herbal remedy that has been marketed as an over-the-counter drug for the treatment of prostate cancer. Anecdotal evidence of greatly reduced prostate-specific antigen (PSA) levels in patients taking this preparation prompted more formal testing of its effect. Laboratory studies show that PC-SPES has the ability to slow growth of both hormone-sensitive and hormone-insensitive prostate cancer cell lines in the test tube. Studies done with mice that have been implanted with prostate cancer cells indicate that the treatment triggers apoptosis (programmed cell death) in the artificially created hormone-insensitive tumors.

PC-SPES was shown in three clinical studies to reduce the serum prostate-specific antigen (PSA) levels in the overwhelming majority of patients suffering from prostate cancer that is unresponsive to androgen therapy. The treatment also reduces prostate acid phosphatase (PAP) levels, an enzyme often elevated with hormone-resistant disease. Treatment with the mixture has been shown to decrease pain, decrease narcotic use, and increase perceived quality of life. Researchers noted bone scan improvements, indicating a reduction in the size of cancer metastases to the bone. The majority of the work with this treatment has been done with patients having advanced disease, characterized by elevated PSA values and Gleason tumor scores.

According to one Japanese study, PC-SPES also shows promise in treating Leukemia.

Description

PC-SPES is a mixture of eight herbs used in Chinese medicine: *Ganoderma lucidum*, *Scutellaria baicalensis*, *Rabdosia rubescens*, *Isatis indigotica*, *Dendranthema morifolium*, *Seronoa repens* (**saw palmetto**), *Panax pseudoginseng*, and *Glycyrrhiza uralensis* (licorice). The "PC" portion of the name stands for prostate cancer, while SPES is Latin for "hope." It has been commercially available since 1996. Manufacturers claim it stimulates the immune system and has anti-tumor activity. The mixture appears to act like estrogen against the tumors, and the side effects are very similar for the two therapies. Yet an analysis using liquid chromatography shows that diethylstilbestrol (DES), estrone, or estradiol are all absent. Additionally, some patients who did not respond to traditional estrogen therapy and alkylating agents did respond to PC-SPES, suggesting the mechanism may be unique from that used by DES or **estramustine** (nitrogen mustard, an alkylating agent). Researchers plan a clinical trial that will directly compare the action of DES and PC-SPES in an effort to compare and contrast the two treatment methods.

Recommended dosage

In the **clinical trials**, PC-SPES was given either in a dosage of nine tablets per day, three before each mealtime or six tablets a day, three before breakfast and three before dinner. As there was essentially no difference in the anti-tumor effect for the studies, six tablets a day might be a recommended starting dosage.

With herbal medications, such as PC-SPES, potency of herb per tablet and recommended dosage may vary from manufacturer to manufacturer.

KEY TERMS

Alkylating agent—A chemical that alters the composition of the genetic material of rapidly dividing cells, such as cancer cells, causing selective cell death; used as a chemotherapeutic agent to treat prostate cancer.

Androgen—Hormones responsible for male characteristics that can be necessary for growth of prostate tumors; blocking the action of androgens can treat prostate cancer.

Apoptosis—An innate process of a cell that brings about its death at the end of the cell's useful lifetime; when malfunctioning can cause cancer.

Gleason grading system—A method of predicting the tendency of a tumor in the prostate to metastasize based on how similar the tumor is to normal prostate tissue; the higher the number the greater the predicted tendency of the tumor to metastasize.

Prostate-specific antigen (PSA)—A protein produced by the cells of the prostate that can be elevated in patients suffering from prostate cancer, abbreviated PSA.

Precautions

As PC-SPES has been used only in relatively small clinical trials, the full spectrum of precautions has yet to be determined. The clinical trials required taking the tablets on an empty stomach. Furthermore, despite the small sample size, experience does suggest that patients with known heart disease or stroke tendencies should take this medicine with caution, as it might aggravate these conditions.

Side effects

The side effects for PC-SPES are relatively mild and include, from most frequent to least frequent, nipple tenderness, **nausea and vomiting**, **diarrhea**, **fatigue**, gynecomastia (swelling of the male breast), leg cramps or swelling, angina, increased hot flashes, and blood clots. The incidence of angina occurred in a patient with preexisting coronary disease and was treated by altered heart medications and a reduction in PC-SPES administered.

Interactions

There have been no studies of drug interactions between PC-SPES and other medications. The lack of information about potential adverse interactions suggests caution in adding PC-SPES to other more traditional treatment methods for prostate cancer.

Resources

PERIODICALS

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National Center for Complementary and Alternative Medicine (NCCAM) Clearinghouse. P. O. Box 7923, Gaithersburg, MD 20898. (888) 644-6226. <http://nccam.nih.gov>.

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Michelle Johnson, M.S., J.D.
Rebecca J. Frey, Ph.D.

Pegaspargase

Definition

Pegaspargase (also known as PEG-L-asparaginase and Oncaspar) is a medicine used to stop growth of cancer and formation of new cancer cells.

Purpose

Pegaspargase is used as part of induction regimen for the treatment of **acute lymphocytic leukemia** (ALL) in children who developed an allergy to **asparaginase**.

Description

Pegaspargase is a slightly changed version of the native form of asparaginase (*E. coli* asparaginase) that is linked to polyethylene glycol (PEG) molecule. This medicine was made available in 1994 under the brand name Oncaspar. It is more expensive than the native form and is mainly used in patients who developed an allergy to the native form. The advantage of pegaspargase over asparaginase is that it is less likely to cause an allergic reaction and has a longer duration in the body and can be given less frequently. Pegaspargase kills cancer cells by depleting a certain amino acid in the blood (L-asparagine), which is needed for survival and growth of tumor cells in patients with acute lymphocytic leukemia. Fortunately, normal cells can make their own L-asparagine and are not dependent on L-asparagine from the blood for survival.

Pegaspargase is mainly given in combination with other drugs **vincristine** (a vinca alkaloid anticancer drug) and steroids (either prednisone or **dexamethasone**). Other **chemotherapy** medicines are added to this regimen if a patient is at a high risk for disease recurrence.

Recommended dosage

Adults and children with body surface area greater than 0.6 square meters

In induction chemotherapy for acute lymphocytic leukemia, doses vary between different chemotherapy protocols. The usual dose is 2500 international units (IU) per square meter of body surface area given every 14 days.

Children with body surface area less than 0.6 square meters

In induction chemotherapy for acute lymphocytic leukemia, the usual dose is 82.5 IU per kg given every 14 days.

Administration

This medicine can be given directly into the muscle (intramuscular) or into the vein (intravenous). Intramuscular injection of pegaspargase is preferred over the intravenous route because of lower risk of liver disease, blood clotting problems, stomach, and kidney problems. When used intramuscularly, it must be administered as deep injection into a large muscle. When given intravenously, it must be infused over one to two hours. Patients will be monitored closely by a physician for 30 to 60 minutes.

Precautions

The use of this medication should be avoided in patients with active pancreatitis (inflammation of the pancreas) or history of pancreatitis and in patients who have had a serious allergic reaction to pegaspargase in the past.

Pegaspargase should only be administered in a hospital, and a patient will need to be observed by a physician for the first hour.

This medication can lower the body's ability to fight infections. Patients should avoid contact with any individuals that may have a cold, flu, or other infection.

Pegaspargase should be used with caution in the following populations:

- People with gout (it may increase uric acid levels and worsen gout).
- People with diabetes (it may increase blood sugar).
- Breast-feeding mothers (it is not known if asparaginase crosses into breast milk).
- Women who are pregnant or may become pregnant (unless benefits to the mother outweigh the risks to the baby).

Patients should contact a doctor immediately if any of these symptoms develop:

- **fever**, chills, sore throat
- chest pain or heart palpitations
- yellowing of the skin or eyes
- puffy face, skin rash, trouble breathing, joint pain
- drowsiness, confusion, hallucinations, convulsions
- unusual bleeding or bruising
- stomach pain with nausea and vomiting, and loss of appetite (anorexia)

A physician will be doing blood tests before starting therapy and during therapy to monitor complete blood count, blood sugar, pancreas, kidney, and liver functions.

Side effects

Pegaspargase is a very potent medicine that can cause serious side effects. An allergic reaction with skin rash, **itching**, joint pain, puffy face, and difficulty breathing is a side effect that happens very quickly after the drug is injected. The allergic reaction to pegaspargase is less common than with asparaginase. The severe type of this allergic reaction (anaphylaxis) can result in death. Other common side effects include nausea, vomiting, **diarrhea**, loss of appetite, stomach cramps, yellow-

KEY TERMS

Acute lymphocytic leukemia (ALL)—This is the most common cancer in children. Patients with ALL can present with fever, weakness, fatigue, pallor, unusual bleeding and easy bruising, pinpoint dots on the skin, large lymph nodes, and large liver and spleen. ALL in children has a much better prognosis than in adults, with over 90% of children going into remission and an over 80% cure rate with chemotherapy.

Induction therapy—The first stage in treatment of ALL. The purpose of this stage is to quickly cause remission of the disease. The combination of vincristine, asparaginase, and steroids make up the foundation of induction regimen.

Nonsteroidal anti-inflammatory drugs (NSAIDS)—Drugs such as ibuprofen (Advil, Motrin) and naproxen (Aleve) that reduce pain, fever, and inflammation.

ing of the eyes or skin, swelling of hands or feet, and pain at the injection site. Less frequent side effects include high blood sugar, chest pain, heart palpitations, headache, chills, **night sweats**, convulsions, decreased kidney function, increased blood clotting, mouth sores, and decreased body's ability to fight infections. Usually the side effects of pegaspargase are more severe in adults than in children.

Interactions

Pegaspargase can decrease effectiveness of **methotrexate** (an antimetabolite, or compound that prevents the synthesis and utilization of normal cellular metabolite, anticancer drug) in killing cancer cells when given right before and together with methotrexate. The use of these two medicines together should be avoided.

Pegaspargase can decrease breakdown and increase toxicity of **cyclophosphamide** (a DNA alkylating anticancer drug).

Risk of liver disease may be increased in patients getting both pegaspargase and **mercaptopurine** (a purine analog antimetabolite anticancer drug).

This medicine can increase blood sugar, especially when given with steroids.

Pegaspargase should be given after vincristine instead of before or with vincristine because it can increase the risk of numbing, tingling, and pain in hands and feet.

People taking blood thinners (**warfarin**, **heparin**, or its derivatives), aspirin, and non-steroidal anti-inflammatory drugs (ibuprofen, naproxen) may be at an increased risk of bleeding. A physician and a pharmacist must be informed about any prescription or over-the-counter medications the patient is taking.

Olga Bessmertny, Pharm.D.

PEG-L-asparaginase *see* **Pegaspargase**

Pemetrexed

Definition

Pemetrexed is an anticancer drug that is used to treat malignant pleural **mesothelioma** and **non-small cell lung cancer**.

Purpose

Malignant pleural mesothelioma (MPM) is a rare type of cancer of the mesothelium (the lining of the chest cavity around the lungs and the abdomen). About 2,000–2,500 new cases of MPM are diagnosed in the United States annually. Twice that many cases occur in Europe. MPM usually is caused by exposure to asbestos. Inhaled asbestos fibers attach to the outer lining of the lung and the chest wall, causing tumor growth. The disease takes years to develop after asbestos exposure. Symptoms of MPM usually are not apparent or are misdiagnosed until after the disease is well-advanced and difficult to treat with surgery or **radiation therapy**. Average survival time is 9–13 months after diagnosis. Pemetrexed is used for patients with MPM that cannot be treated surgically.

Lung cancer—usually caused by smoking—is the most common cause of cancer death in the United States. Almost 174,000 people develop lung cancer each year and more than 160,000 die from it annually. Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancers and includes squamous cell **carcinoma**, **adenocarcinoma**, and large cell carcinoma. Pemetrexed is used to treat stage III or IV NSCLC in patients whose cancer has recurred following **chemotherapy** and is advancing or has spread (metastasized). Pemetrexed does not improve rates of survival over the standard second-line treatment drug **docetaxel** but has fewer side effects and thus may improve the quality of life. Neither drug cures recurrent lung cancer.

Description

During the 1980s a new class of drugs called multi-targeted anti-folates (MTA) were developed. These drugs limited the ability of cancer cells to obtain **folic acid**, a member of the B-vitamin complex that is required for cell growth and reproduction. However, these drugs were considered too toxic to use until pemetrexed was discovered by a Princeton University biochemist in the 1990s.

Pemetrexed disodium heptahydrate (Alimta), manufactured by Eli Lilly, was approved by the U.S. Food and Drug Administration (FDA) in February of 2004 for use in combination with the anticancer drug **cisplatin** to treat MPM. Pemetrexed, also known as LY231514, was the first drug for treating this type of cancer and, as an orphan drug for a rare disease, received priority review from the FDA. The Orphan Drug Act granted Eli Lilly seven years of exclusive marketing. In August of 2004 the FDA approved pemetrexed for the treatment of NSCLC.

Pemetrexed is a member of a large group of chemotherapy drugs known as antineoplastics or antimetabolites; it sometimes is referred to as an antifolate antineoplastic agent. It inhibits three folate-dependent enzymes that mesothelioma and lung cancer cells need for the synthesis of the nucleotides that make up DNA and RNA. Fast growing cancer cells have a much higher requirement for nucleotides than normal cells.

Effectiveness

The effectiveness of pemetrexed for treating MPM was established in a single clinical trial with 448 patients, comparing combined treatment with pemetrexed and cisplatin to treatment with cisplatin alone. Patients receiving the combined treatment lived three months longer than those receiving cisplatin alone—12 months versus nine months. Patients also had improved lung function. Tumors shrank in 41% of the patients treated with the combined drugs, compared with 17% of those treated with cisplatin alone.

In an earlier clinical trial pemetrexed combined with the chemotherapy drug **carboplatin**, which is similar to cisplatin, increased the average survival time of mesothelioma patients to 15 months and some patients were still alive after nearly three years. More than two-thirds of the treated patients had reduced pain and improvement in other symptoms. Tumors shrank in almost one-third of the patients.

In a clinical trial of 571 patients with recurrent NSCLC, those treated with either pemetrexed or docetaxel had a one-year survival rate of 30%; however, those receiving pemetrexed were significantly less likely to experience the following:

- fever
- infections
- hospitalizations
- hair loss
- numbness in the arms and legs

Recommended dosage

Pemetrexed is supplied as a sterile powder in single-dose vials of 500 mg pemetrexed and 500 mg mannitol. Pemetrexed is given in a single 10-minute intravenous infusion, once every three weeks. The dose depends on body size and may be adjusted or delayed depending on the patient's blood counts, kidney and liver function, and general condition.

For treating MPM, cisplatin is infused for two hours, beginning about 30 minutes after the end of pemetrexed infusion. As much fluid as possible is taken before and after treatment with cisplatin to keep the kidneys functioning properly. Intravenous fluids usually are given during cisplatin infusion.

Since pemetrexed interferes with both folic acid and vitamin B_{12}, these nutrients are always taken as supplements to prevent severe side effects. Folic acid—350–1000 micrograms—is taken every day for at least five out of seven days prior to pemetrexed treatment. It is continued daily until 21 days after the final treatment. Folic acid is available over-the-counter as well as in many multivitamins. Vitamin B12 is injected during the week before the first pemetrexed treatment and once every nine weeks during treatment.

Patients also take a corticosteroid such as **dexamethasone** twice a day for three days, beginning the day before pemetrexed infusion, to lower the risk of skin reactions.

Precautions

Pemetrexed causes birth defects if administered to a woman during the conception period or during pregnancy or to a man near the time of conception. Birth control must be used by patients while they receive pemetrexed treatment. Women should not breastfeed while being treated with pemetrexed. Like many other chemotherapy drugs, pemetrexed may cause sterility.

Medical conditions that may interfere with the use of pemetrexed include the following:

- chicken pox or exposure to chicken pox
- gout

- heart disease
- congestive heart failure
- shingles
- kidney stones or kidney disease
- liver disease
- third space fluid (extra body fluid such as **ascites** in the stomach area or **pleural effusion** in the lungs and chest)
- other types of cancer

Other precautions during pemetrexed treatment include avoiding the following:

- touching the eyes or inside of the nose without first washing the hands
- cuts or bleeding
- contact sports, bruising, or injury

It is important to avoid vaccinations during and after pemetrexed treatment. It also is important to avoid contact with those who have taken oral polio vaccine within the past several months. A protective face mask that covers the nose and mouth may be used if contact is unavoidable. If possible, people with any infection should be avoided.

Side effects

Pemetrexed has fewer side effects than many anticancer drugs; however, the most common side effects are as follows:

- anemia (low red blood cell count) that may cause **fatigue**, paleness, or shortness of breath
- a temporary decline in white blood cells, particularly during the first 10–14 days after each treatment
- a decline in blood platelets
- nausea and vomiting
- diarrhea
- constipation
- loss of appetite
- weight loss
- heartburn
- dry mouth
- redness or sores in the mouth or throat or on the lips a few days after treatment
- rash or **itching** between treatments
- wrinkled or peeling skin
- burning, tingling, numbness, or pain in the extremities
- muscle aches, cramping, stiffness, or pain
- joint swelling or pain
- difficult or rapid breathing
- pain or burning in the throat
- difficult or painful swallowing
- stuffy or runny nose
- sunken eyes
- irritability
- mood swings or depression
- lightheadedness or dizziness
- confusion
- insomnia
- difficulty concentrating
- hair loss
- increased heart rate
- decreased urination

KEY TERMS

Cisplatin—An anticancer drug that is used together with pemetrexed to treat MPM.

Docetaxel—An anticancer drug, belonging to the drug family called mitotic inhibitors, that was the standard treatment for recurrent NSCLC prior to pemetrexed.

Folic acid, folate—A member of the vitamin B complex that is a required cell nutrient.

Malignant pleural mesothelioma, MPM—A cancer of the mesothelium that lines the chest cavity; caused by exposure to asbestos.

Multitargeted anti-folate, MTA—A drug that targets various folate-dependent enzymes.

Non-small cell lung cancer, NSCLC—The most common type of lung cancer; includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

Orphan drug—A drug that treats a rare condition; such drugs receive special treatment by the FDA under the Orphan Drug Act.

Vitamin B12—Cobalamin; a protein complex of animal origin that is required for the formation of red blood cells.

White blood cells (WBC)—Blood cells, including lymphocytes, neutrophils, eosinophils, marcrophages, and mast cells, that are produced in the bone marrow and help the body fight infection and disease.

- severe weakness and fatigue for a few days after treatment
- liver problems, as indicated by fluctuating liver function blood tests

Blood counts are taken before and after each pemetrexed treatment. Rare side effects of pemetrexed include a severe allergic reaction or blood clots.

Pemetrexed suppresses production of blood cells by the bone marrow and decreases the white blood cell count. Symptoms of infection caused by decreased white blood cells include the following:

- fever above 100.5°F (38°C)
- chills
- cough
- hoarseness
- lower back or side pain
- difficult or painful urination

Pemetrexed can reduce blood platelets, thereby increasing the risk of the following:

- unusual bleeding or bruising
- nosebleeds
- bleeding gums when teeth are being cleaned
- black, tarry stools
- tiny red spots on the skin
- blood in the urine or stool

Other serious side effects of pemetrexed can include:

- swollen glands
- increased thirst
- swelling of the eyes, face, fingers, or lower legs
- pain in the chest, groin, or legs, especially in the calves
- sudden severe headaches
- sudden changes in vision
- sudden slurred speech
- fast or irregular breathing
- chest tightness or wheezing
- increased blood pressure
- loss of coordination
- fainting or loss of consciousness
- weight gain

Interactions

Known interactions of pemetrexed with other drugs include:

- oral contraceptives
- vitamins and herbal supplements
- nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen such as Motrin, naproxen such as Aleve, celecoxib (Celebrex), rofecoxib (Vioxx)

Margaret Alic, Ph.D.

Penile cancer

Definition

Penile cancer is the growth of malignant cells on the external skin and in the tissues of the penis.

Description

Penile cancer is a disease in which cancerous cells appear on the penis. If left untreated, this cancer can grow and spread from the penis to the lymph nodes in the groin and eventually to other parts of the body.

Demographics

Penile cancer is a rare form of cancer that develops in about one out of 100,000 men per year in the United States. Penile cancer is more common in other parts of the world, particularly Africa and Asia. In Uganda, penile cancer is the most common form of cancer for men.

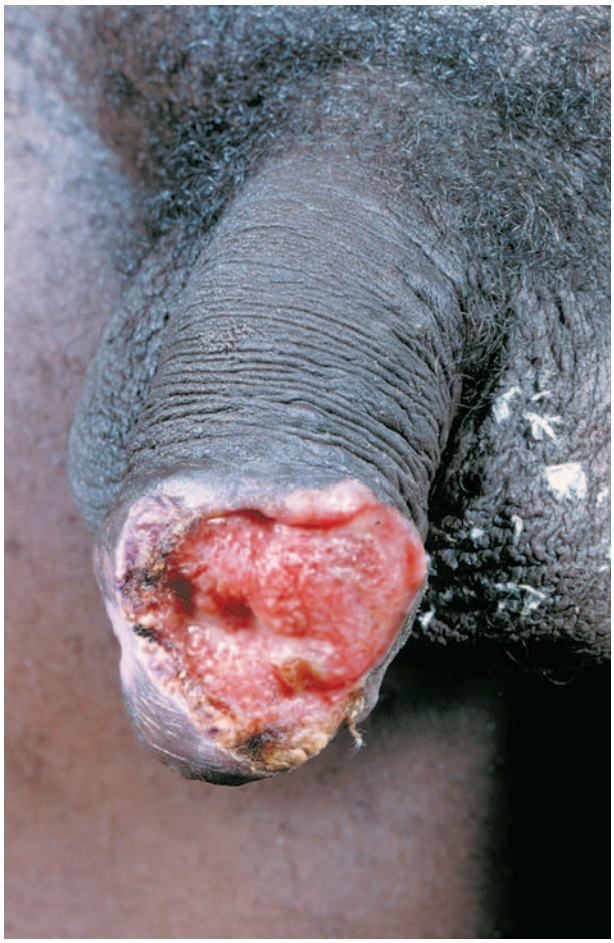
Causes and symptoms

The cause of penile cancer is unknown. The most common symptoms of penile cancer are:

- A tender spot, an open sore, or a wart-like lump on the penis.
- unusual liquid discharges from the penis.
- Pain or bleeding in the genital area.

Diagnosis

In order to diagnose penile cancer, the doctor examines the patient's penis for lumps or other abnormalities. A tissue sample, or **biopsy**, may be ordered to distinguish cancerous cells from syphilis and penile warts. If the results confirm a diagnosis of cancer, additional tests are done to determine whether the disease has spread to other parts of the body.



Carcinoma of penis. *(Custom Medical Stock Photo. Reproduced by permission.)*

Treatment team

A doctor who specializes in the genitourinary tract (urologist) is usually the first point of contact for the patient and makes the diagnosis of penile cancer. Once a diagnosis of cancer is made, a specialist in cancer (oncologist) will become involved to determine the stage of the cancer and recommend appropriate treatments.

Clinical staging, treatments, and prognosis

In Stage I penile cancer, malignant cells are found only on the surface of the head (glans) and on the foreskin of the penis. If the cancer is limited to the foreskin, treatment may involve wide local excision and circumcision. Wide local excision is a form of surgery that removes only cancer cells and a small amount of normal tissue adjacent to them. Circumcision is removal of the foreskin.

If the Stage I cancer is only on the glans, treatment may involve the use of a **fluorouracil** cream (Adrucil, Efudex), and/or microsurgery. Microsurgery removes cancerous tissue and the smallest possible amount of normal tissue. During microsurgery, the doctor uses a special instrument that provides a comprehensive view of the area where cancer cells are located and makes it possible to determine that all malignant cells have been removed.

In Stage II, the penile cancer has spread to the surface of the glans, tissues beneath the surface, and the shaft of the penis. The treatment recommended may be **amputation** of all or part of the penis (total or partial penectomy). If the disease is diagnosed early enough, surgeons are often able to preserve enough of the organ for urination and sexual activity. Treatment may also include microsurgery and external **radiation therapy**, in which a machine provides radiation to the affected area. Laser surgery is an experimental treatment for Stage II cancers. Laser surgery uses an intense precisely focused beam of light to dissolve or burn away cancer cells.

In Stage III, malignant cells have spread to lymph nodes in the groin, where they cause swelling. The recommended treatment may include amputation of the penis and removal of the lymph nodes on both sides. Radiation therapy may also be suggested. More advanced disease requires systemic treatments using drugs (**chemotherapy**). In chemotherapy, medicines are administered intravenously or taken by mouth. These drugs enter the bloodstream and kill cancer cells that have spread to any part of the body.

In Stage IV, the disease has spread throughout the penis and lymph nodes in the groin, or has traveled to other parts of the body. Treatments are similar to that for Stage III cancer.

Recurrent penile cancer is disease that recurs in the penis or develops in another part of the body after treatment has eradicated the original cancer cells.

Cure rates are high for cancers diagnosed in Stage I or II, but much lower for Stages III and IV, by which time cancer cells have spread to the lymph nodes.

Alternative and complementary therapies

In addition to the treatments previously described, biological therapy is another treatment that is currently being studied. Biological therapy is a type of treatment that is sometimes called biological response modifier (BRM) therapy. It uses natural or artificial substances to boost, focus, or reinforce the body's disease-fighting resources.

Coping with cancer treatment

Medical side effects of treatment include constipation, **fatigue**, and sleep disorders. These effects may be

KEY TERMS

Circumcision—Surgical removal of the foreskin of the penis. It is usually performed shortly after birth.

Fluorouracil—A cell-killing (cytotoxic) medication that can be applied in cream form to treat cancer of the penis.

QUESTIONS TO ASK THE DOCTOR

- What stage is my cancer?
- What treatment alternatives do I have?
- Do I qualify for an experimental trial of a new treatment?

managed through a combination of diet and environment as well as supplemental drug treatments. The patient should seek support resources for the psychological effects that treatment for penile cancer may cause, such as **depression**, decreased **sexuality**, anxiety, or feelings of grief.

Clinical trials

New treatments for penile cancer that are in **clinical trials** include chemotherapy with the drugs **methotrexate**, **bleomycin**, interferon, or **cisplatin**.

Prevention

Conditions which increase a person's chance of getting penile cancer include:

- Infection with genital warts (human papillomavirus, or HPV).
- a skin disease called psoriasis
- a condition called phimosis, in which the foreskin becomes difficult to retract
- other conditions that result in repeated irritation of the penis
- a history of smoking

There appears to be a connection between development of the disease and lack of personal hygiene. Failure to regularly and thoroughly cleanse the part of the penis covered by the foreskin increases the risk of developing the disease. Penile cancer is also more common in uncircumcised men.

Special concerns

The treatment or amputation of the penis may have a significant psychological impact on the patient. Thorough patient education and appropriate counseling or support resources are a must.

See also Testicular cancer.

Resources

ORGANIZATIONS

American Cancer Society. (800) ACS-2345. <http://www.cancer.org/>.

The Cancer Group Institute. 17620 9th Ave. NE, North Miami Beach, Florida 33162. (305) 493-1980. <http://www.cancergroup.com>.

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Pentamidine *see* **Antibiotics**

Pentostatin

Definition

Pentostatin is an anticancer (antineoplastic) agent belonging to the class of drugs called antimetabolites (compounds that prevent the synthesis and utilization of normal cellular metabolite). It is a natural product isolated from *Streptomyces antibioticus*. It also acts as a suppressor of the immune system. It is available under the brand name Nipent. Other common names for pentostatin include 2'-deoxycoformycin and 2'DCF.

Purpose

Pentostatin is primarily used to treat a particular type of cancer of the blood called **hairy cell leukemia**. It is also used in the treatment of low-grade lymphomas. **Clinical trials** are underway to determine the effectiveness of pentostatin in fighting **cutaneous T-cell lymphoma** (CTCL), **chronic lymphocytic leukemia** (CLL), **non-Hodgkin's lymphomas** (NHL), and prolymphocytic leukemia.

Description

Pentostatin chemically interferes with the synthesis of genetic material (DNA and RNA) of cancer cells, which prevents these cells from being able to reproduce and continue the growth of the cancer.

Recommended dosage

Pentostatin may be taken only as an injection. It is generally given once every two weeks. A typical dosage is four mg per square meter of body surface area. However, the dosage prescribed can vary widely depending on the patient, the cancer being treated, and whether or not other medications are also being taken.

Precautions

Pentostatin should be taken on an empty stomach. If stomach irritation occurs, it should be taken with small amounts of food or milk. Pentostatin should always be taken with plenty of fluids.

Pentostatin can cause an allergic reaction in some people. Patients with a prior allergic reaction to pentostatin should not take pentostatin.

Pentostatin can cause serious birth defects if either the man or the woman is taking this drug at the time of conception or if the woman is taking this drug during pregnancy.

Because pentostatin is easily passed from mother to child through breast milk, breast feeding is not recommended while pentostatin is being taken.

Pentostatin suppresses the immune system and interferes with the normal functioning of certain organs and tissues. For these reasons, it is important that the prescribing physician is aware of any of the following preexisting medical conditions:

- a current case of, or recent exposure to, chicken pox
- herpes zoster (shingles)
- a current case, or history of, gout or kidney stones
- all current infections
- kidney disease.
- liver disease

Also, because pentostatin is such a potent immunosuppressant, patients taking this drug must exercise extreme caution to avoid contracting any new infections. They should do their best to:

- avoid any person with any type of infection
- avoid bleeding injuries, including those caused by brushing or flossing the teeth
- avoid contact of the hands with the eyes or nasal passages (inside of the nose) unless the hands have just been washed and have not touched anything else since this washing
- avoid contact sports or any other activity that could cause a bruising or bleeding injury

KEY TERMS

Antineoplastic—A drug that prevents the growth of a neoplasm by interfering with the maturation or proliferation of the cells of the neoplasm.

Hairy cell leukemia—A rare form of cancer in which hairy cells grow out of control in the blood, liver, and spleen.

Lymphoma—A malignant tumor of the lymphatic system.

Neoplasm—New abnormal growth of tissue.

Side effects

The most common side effects of pentostatin are: cough, extreme **fatigue**, increased susceptibility to infection, loss of appetite (anorexia), skin rash or **itching**, nausea, temporary hair loss (alopecia), vomiting, and **weight loss**.

Less common side effects include anxiety or nervousness; changes in vision; nosebleed; sores in the mouth or on lips; sore, red eyes; trouble sleeping (insomnia); numbness or tingling in the hands and/or feet; and swelling in the feet or lower legs.

A doctor should be consulted immediately if the patient experiences shortness of breath, chest or abdominal pain, persistent cough, **fever** and chills, pain in the lower back or sides, painful or difficult urination, unusual bleeding or bruising, blood in the urine or stool, or tiny red dots on the skin.

Interactions

Pentostatin should not be taken in combination with any prescription drug, over-the-counter drug, or herbal remedy without prior consultation with a physician. It is particularly important that the prescribing physician be aware of the use of any of the following drugs or any **radiation therapy** or **chemotherapy** medicine:

- amphotericin B
- antithyroid agents
- azathioprine

- chloramphenicol
- colchicine
- flucytosine
- fludarabine
- ganciclovir
- interferon
- plicamycin
- probenecid
- sulfinpyrazone
- vidarabine
- zidovudine

Paul A. Johnson, Ed.M.

Percutaneous transhepatic cholangiography

Definition

Percutaneous transhepatic cholangiography (PTHC) is an x-ray test used to identify obstructions either in the liver or bile ducts that slow or stop the flow of bile from the liver to the digestive system.

Purpose

Because the liver and bile ducts are not normally seen on x rays, the doctor injects the liver with a special dye that will show up on the resulting picture. This dye distributes evenly to fill the whole liver drainage system. If the dye does not distribute evenly, this is indicative of a blockage, which may caused by a gallstone or a tumor in the liver, bile ducts, or pancreas.

Precautions

Patients should report allergic reactions to:

- anesthetics
- dyes used in medical tests
- iodine
- shellfish

PTHC should not be performed on anyone who has cholangitis (inflammation of the bile duct), massive **ascites**, a severe allergy to iodine, or a serious uncorrectable or uncontrollable bleeding disorder. Patients who have diabetes should inform their doctors.

Description

PTHC is performed in a hospital, doctor's office, or outpatient surgical or x-ray facility. The patient lies on a movable x-ray table and is given a local anesthetic. The patient will be told to hold his or her breath, and a doctor, nurse, or laboratory technician will inject a special dye into the liver as the patient exhales.

The patient may feel a twinge when the needle penetrates the liver, a pressure or fullness, or brief discomfort in the upper right side of the back. Hands and feet may become numb during the 30-60 minute procedure.

The x-ray table will be rotated several times during the test, and the patient helped to assume a variety of positions. A special x-ray machine called a fluoroscope will track the dye's movement through the bile ducts and show whether the fluid is moving freely or if its passage is obstructed.

PTHC costs about $1,600. The test may have to be repeated if the patient moves while x rays are being taken.

Preparation

An intravenous antibiotic may be given every 4–6 hours during the 24 hours before the test. The patient will be told to fast overnight. Having an empty stomach is a safety measure in case of complications, such as bleeding, that might require emergency repair surgery. Medications such as aspirin, or non-steroidal anti-inflammatory drugs that thin the blood, should be stopped for some three to seven days prior to taking the PRHC test. Patients may also be given a sedative a few minutes before the test begins.

Aftercare

A nurse will monitor the patient's vital signs and watch for:

- itching
- flushing
- nausea and vomiting
- sweating
- excessive flow of saliva
- possible serious allergic reactions to contrast dye

The patient should stay in bed for at least six hours after the test, lying on the right side to prevent bleeding from the injection site. The patient may resume normal eating habits and gradually resume normal activities. The doctor should be informed right away if pain develops in the right abdomen or shoulder or in case of **fever**, dizziness, or a change in stool color to black or red.

KEY TERMS

Ascites—Abnormal accumulation of fluid in the abdomen.

Bile ducts—Tubes that carry bile, a thick yellowish-green fluid that is made by the liver, stored in the gallbladder, and helps the body digest fats.

Cholangitis—Inflammation of the bile duct.

Fluoroscope—An x-ray machine that projects images of organs.

Granulomatous disease—Characterized by growth of tiny blood vessels and connective tissue.

Jaundice—Disease that causes bile to accumulate in the blood, causing the skin and whites of the eyes to turn yellow. Obstructive jaundice is caused by blockage of bile ducts, while non-obstructive jaundice is caused by disease or infection of the liver.

Risks

Septicemia (blood poisoning) and bile peritonitis (a potentially fatal infection or inflammation of the membrane covering the walls of the abdomen) are rare but serious complications of this procedure. Dye occasionally leaks from the liver into the abdomen, and there is a slight risk of bleeding or infection.

Normal results

Normal x rays show dye evenly distributed throughout the bile ducts. Obesity, gas, and failure to fast can affect test results.

Abnormal results

Enlargement of bile ducts may indicate:

- obstructive or non-obstructive jaundice
- cholelithiasis (gallstones)
- hepatitis (inflammation of the liver)
- cirrhosis (chronic liver disease)
- granulomatous disease
- pancreatic cancer
- bile duct or gallbladder cancers

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Maureen Haggerty

Pericardial effusion

Definition

A pericardial effusion is a fluid collection that develops between the pericardium, the lining of the heart, and the heart itself. Pericardial effusions can be found in up to 20% of cancer patients at autopsy, but of those, only about 30% would have had symptoms from their effusions.

Description

Most of the organs of the body are covered by thin membranes. The membrane that surrounds the heart is called the pericardium. Normally, only a few milliliters of fluid sit between the pericardium and the muscle of the heart. Any larger, abnormal collection of fluid in that space is called a pericardial effusion.

A pericardial effusion can interfere with the normal contraction and expansion of the heart muscle, which decreases the heart's ability to pump blood effectively. A large or rapidly developing effusion can cause a condition called cardiac tamponade. Tamponade is a medical emergency and can be fatal if not diagnosed and treated promptly. Symptoms of tamponade include shortness of breath, rapid pulse, cough, and chest discomfort. As tamponade progresses, low blood pressure and shock develop and cardiac arrest can follow.

A smaller or more slowly developing pericardial effusion also causes chest discomfort. Other symptoms, such as shortness or breath, difficulty swallowing, hoarseness or hiccups result from pressure from the enlarged, fluid-filled pericardium pressing against nearby organs. Although chronic or smaller effusions are not emergencies, they do cause discomfort and can become more serious.

The diagnosis of pericardial effusion is made on the basis of patient history, physical examination and appropriate laboratory studies. Heart sounds can be muffled, the veins in the neck engorged and the pulse rapid. A chest **x ray** shows enlargement of the silhouette of the heart. An echocardiogram or cardiac ultrasound will show the fluid surrounding the heart, as will CT and MRI scans.

Causes

A pericardial effusion in a cancer patient is caused either by the disease itself or by the treatment for the disease.

Many cancers can metastasize or spread to the pericardium or the heart itself. They include:

- Lung
- Breast
- Thyroid
- Esophagus
- Kidney
- Pancreas
- Endometrium
- Larynx
- Cervix
- Stomach
- Mouth
- Liver
- Ovary
- Colon
- Prostate
- Leukemia
- Melanoma
- **Lymphoma**
- Sarcoma
- Myeloma

The presence of the cancerous cells on the pericardium is an irritant and causes a reactive fluid buildup, much as a blister forms under the skin due to irritation. Some cancers cause less fluid buildup, instead thickening the pericardium and making it less elastic. This can also cause symptoms of tamponade.

Another cause of pericardial effusion in a cancer patient is previous **radiation therapy** to the chest, especially in the case of lung cancer or lymphoma. While such effusions are less likely to produce tamponade, it is possible.

Many of the drugs that are used to treat cancer can cause pericardial disease and can thus potentially cause pericardial effusions. Some of the chemotherapeutic drugs that can affect the pericardium are **cytarabine**, **fluorouracil**, **cyclophosphamide**, **doxorubicin** and **daunorubicin**. Granulocyte-macrophage colony-stimulating factor (**sargramostim**), often given to help increase the population of white blood cells during intensive **chemotherapy**, is also a pericardial irritant.

Other causes of pericardial effusions are heart failure, liver disease, and kidney disease. Any of these can also affect cancer patients.

Treatments

Treatment of pericardial effusion depends on the presence or absence of cardiac tamponade. Tamponade is a medical emergency and symptoms such as cyanosis, a blue tinge to the lips and skin, shock, or a change in mental status require urgent drainage of the fluid. This drainage is accomplished with a procedure called **pericardiocentesis**, in which a needle is inserted into the pericardial space and the fluid withdrawn into a large syringe. Chronic effusions can be drained electively, and some need not be drained at all. If a patient's prognosis is poor and the pericardial effusion is not compromising the function of the heart, the risks of a drainage procedure may outweigh its benefits and the effusion may be left alone. Effusions caused by lymphoma often resolve after aggressive chemotherapy and need no further treatment.

Elective drainage of a pericardial effusion is done by one of several surgical procedures. The surgeon might open the chest, make a small incision under the bottom of the breastbone, or use a video-assisted technique called **thoracoscopy**. In addition to permitting drainage of the pericardial fluid, these procedures permit the surgeon to take a pericardial **biopsy**, which can confirm the diagnosis of metastatic cancer.

Sometimes a catheter is placed in the pericardium and connected to an external drainage system to collect any fluid that might reaccumulate.

Occasionally, sclerosing agents—drugs that cause scarring—are infused into the pericardium through a catheter. These agents, such as tetracycline, minocycline or **bleomycin**, irritate the pericardium, causing it to thicken and adhere to the heart muscle. This scarring prevents the further accumulation of fluid. Some malignant pericardial effusions resolve after the instillation of chemotherapeutic drugs such as **thiotepa** or platinum directly into the pericardial cavity. Others resolve after radiation therapy directed at the pericardium.

Alternative and complementary therapies

No complementary or alternative treatments are aimed specifically at treating pericardial effusions, but

KEY TERMS

Pericardium—The thin membrane that surrounds the heart.

Sclerosing agents—Drugs that are instilled into parts of the body to deliberately induce scarring.

Tamponade—A medical emergency in which fluid or other substances between the pericardium and heart muscle compress the heart muscle and interfere with the normal pumping of blood.

Thoracoscopy—Chest surgery done with the guidance of special video cameras that permit the surgeon to see inside the chest.

practitioners of acupressure and acupuncture designate a pressure point for the pericardium at two and a half finger breadths above the wrist crease on the inner aspect of the arm. Acupressure and acupuncture do offer some relief of symptoms to those suffering from shortness of breath and might offer benefit to those with pericardial effusions.

See also Pericardiocentesis.

Resources

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Marianne Vahey, M.D.

Pericardiocentesis

Definition

Pericardiocentesis is a therapeutic and diagnostic procedure in which fluid is removed from the pericardium, the sac that surrounds the heart.

Purpose

The pericardium normally contains only a few milliliters (less than a teaspoon) of fluid to cushion the heart. Many illnesses cause larger volumes of fluid, called pericardial effusions, to develop. Spread of cancer to the pericardium is a frequent cause of pericardial effusions. If an effusion is too large, pressure develops within the sac that can interfere with the normal pumping action of the heart. Should that interference become severe, a life-threatening condition called cardiac tamponade can develop, which can lead to shock or death.

Pericardiocentesis is a procedure to remove that fluid, which allows the heart to pump normally again. The fluid is analyzed for the presence of cancer cells or microorganisms. If cardiac tamponade is present, pericardiocentesis must be done on an urgent basis. If tamponade is not present, an elective surgical pericardial drainage procedure can be scheduled.

Precautions

The presence of tamponade is a medical emergency and requires urgent treatment. The blood pressure can be low and breathing compromised. Fluids and intravenous medications might be needed to raise the blood pressure until the pericardiocentesis can be performed.

Description

When possible, pericardiocentesis is performed in the cardiac catheterization laboratory of the hospital, but it can be done at the bedside or in the emergency department. The patient lies on his or her back with the head elevated at about 45 degrees. The skin is sterilized and local anesthetic given. A long needle attached to a large sterile syringe is inserted under the breastbone into the pericardium. If available, an echocardiogram or cardiac ultrasound is done to guide the physician to the pericardium. Once the needle is in the pericardium, the doctor withdraws the pericardial fluid into the syringe. The fluid can then be tested for cancer cells. If the volume of the fluid is large or likely to reaccumulate, a catheter or drain is placed with one end in the pericardial space and the other outside the chest, attached to a collecting bag.

This can stay in place for several days, until there is no more fluid to drain. After withdrawing either the needle or the catheter, the doctor will apply direct pressure to the site.

If a pericardiocentesis is unsuccessful at draining the **pericardial effusion**, other procedures are available such as percutaneous balloon pericardiotomy, in which a balloon-tipped catheter is inserted through the skin and then used to puncture a hole in the pericardium. This is a painful procedure and should be done under anesthesia. The pericardial fluid is allowed to drain into the chest cavity, into the pleural space, the area between the pleura, the membranes that line the lungs, and the lungs themselves. The pleural space can accommodate more fluid than the pericardium without significant discomfort.

Alternatively, if emergent pericardiocentesis is unsuccessful, the patient can be taken to the operating room for a surgical procedure that will drain the fluid. These elective surgical procedures are similar to pericardiocentesis; however, for open surgical procedures, image guidance is not necessary. These are typically performed under general anesthesia. These procedures present the surgeon with the opportunity to perform a **biopsy** of the pericardium, to confirm the suspicion that the patient's cancer has metastasized there. The operation can also be performed as a thoracoscopic procedure.

Finally, if necessary, a pericardiectomy, sometimes called a pericardial stripping, can be performed. This is a surgical procedure to remove the pericardium and is reserved for the most refractory cases. Pericardiectomy tends to carry more risk than other procedures.

Preparation

For a scheduled pericardiocentesis, a patient will take nothing by mouth for several hours before the procedure. The patient will undergo preoperative blood tests, an electrocardiogram, and an echocardiogram or ultrasound of the heart.

Aftercare

Most patients are admitted to an intensive care unit for monitoring after a pericardial drainage procedure. Frequent checks of blood pressure and pulse will be done, and the neck veins will be examined for bulging. Such bulging might indicate a bleeding complication. If a drain has been placed, the fluid collected will be measured, and the site checked for signs of bleeding or infection. Most patients spend several days in the hospital after pericardial drainage, but a few who do not have drains placed can go home the next day.

Risks

There is about a 5% risk of complications with a pericardiocentesis. These risks include:

- cardiac arrest
- myocardial infarction or heart attack
- abnormal heart rhythms
- laceration or puncture of the heart muscle
- laceration of the coronary arteries
- laceration of the lungs
- laceration of the stomach, colon or liver
- air embolism, in which a pocket of air becomes trapped in a blood vessel, blocking blood flow

When a pericardial effusion is caused by the presence of cancer cells, there is also a risk that the fluid might reaccumulate. Injecting irritants into the pericardial sac can initiate scarring of the pericardium. This causes it to adhere to the surface of the heart and prevents fluid from collecting there again. The irritating or sclerosing agents that are

KEY TERMS

Pericardium—The thin membrane that surrounds the heart.

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Tamponade—A medical emergency in which fluid or other substances between the pericardium and heart muscle compress the heart muscle and interfere with the normal pumping of blood.

Thoracoscopy—Chest surgery done with the guidance of special video cameras that permit the surgeon to see inside the chest.

QUESTIONS TO ASK THE DOCTOR

- What is a pericardiocentesis?
- Why do I need this procedure?
- What are the risks?
- What are the risks of not having a pericardiocentesis?
- What sort of anesthesia will I have?
- What do you expect to find?
- What can I expect after the test?
- How long will I need to stay in the hospital?

instilled into the pericardial space through a catheter include tetracycline, minocycline, and **bleomycin**. The injection of these drugs into the pericardium can cause pain. Sometimes, the simple presence of a drainage catheter will introduce the desired scarring, and this method is preferred, when possible, to the use of the irritant drugs.

Normal results

The most important result is the relief of tamponade or other symptoms of heart failure from excess pericardial fluid. The blood pressure should return to normal, chest pain should be relieved, and breathing should become easier.

The fluid will be analyzed. Normal pericardial fluid is clear, has no cancer cells, no evidence of infection, and fewer than 1,000 white blood cells.

Abnormal results

On rare occasions, the pressure changes surrounding the heart that occur after pericardial drainage can cause temporary worsening of symptoms. This is called pericardial shock.

The most likely cause of a pericardial effusion in a person with cancer is spread of cancer to the pericardium. Thus, the fluid might, upon analysis, contain cancerous cells, high levels of protein, and many white blood cells. This can make the fluid thick and viscous. If the pericardial biopsy is performed, as can be done with a surgical drainage procedure, that biopsy might also reveal the presence of cancer cells.

Resources

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Heart Center Online Home Page. <http://www.heartcenteronline.com/>.

Marianne Vahey, M.D.

Peritoneovenous shunt

Definition

A peritoneovenous shunt (PVS) is a device that is inserted surgically into the body to create a passage between the peritoneum (abdominal cavity) and the jugular vein to treat refractory cases of peritoneal **ascites**. Ascites is a condition in which an excessive amount of fluid builds up within the abdominal cavity.

KEY TERMS

Abdomen—The part of the body which lies between the diaphragm and the rim of the pelvis.

Circulatory system—The circulatory system consists of the heart and blood vessels. It serves as the body's transportation system.

Esophagus—The part of the digestive tract that brings food from the mouth to the stomach.

Jugular veins—Large veins returning the blood from the head to the heart into two branches (external and internal) located on each side of the neck.

Lymph—Colorless liquid that carries the white blood cells in the lymphatic vessels.

Lymphatic system—A subsystem of the circulatory system, it consists of lymphatic fluid, lymphatic vessels, and lymphatic tissues (lymph nodes, tonsils, spleen, and thymus). It returns excess fluid to the blood and defends the body against disease.

Peritoneum—Smooth membrane which lines the cavity of the abdomen and which surrounds the viscera (large interior organs) forming a nearly closed bag.

Peritonitis—Inflammation of the peritoneum.

Vena cava—Very large veins. There are two vena cava in the body. The superior vena cava returns blood from the upper limbs, head, and neck to the heart and the inferior vena cava returns blood from the lower limbs to the heart.

QUESTIONS TO ASK THE DOCTOR

- What are the benefits of PVS for my condition?
- Why is medication not possible?
- What complications are possible?
- What happens if the PVS device gets blocked?
- How experienced is the surgeon with PVS surgery?

Purpose

The abnormal build-up of fluid in the spaces found between the tissues and organs of the abdominal cavity is a common symptom of liver disease such as cirrhosis of the liver, but approximately 10% of the diagnosed cases occur as a side effect of several types of cancers, such as ovarian, gastric, exocrine pancreatic, and colorectal cancers, and **lymphoma**. This condition is known as ascites and it causes pain and discomfort in patients. When doctors can not treat advanced ascites with medication, they recommend an operation such as the PVS procedure as a means to empty the abdomen of the accumulated fluid.

The ascites that results from cancer contains high levels of proteins. It occurs because of functional imbalances in the cells of the organs affected by the cancer and because the walls of the capillaries containing the normal abdominal fluid start leaking. Depending on the type of cancer, there may also be a decrease in the ability of the lymphatic system of the body to absorb fluids.

Precautions

The PVS procedure is restricted to patients with livers that function normally. Additionally, the required veins must be healthy so as to allow the insertion of the shunt device. The PVS insertion is not performed in the following cases:

- patients having undergone previous extensive abdominal surgery
- patients diagnosed with bacterial peritonitis
- patients with diseased veins in the esophagus
- patients with heart disease
- patients with a diseased major organ

In cases of ascites due to cancer (malignant ascites), there is a concern that the use of a PVS could enhance the spread of the cancer. In evaluating a cancer patient as a candidate for a PVS, the risk of cancer spread must be balanced against pain/discomfort relief, quality of life issues, and the expected survival period.

Description

The most common PVS device is the LeVeen shunt, used since the 1970s to relieve ascites due to liver disease and since the 1980s for cancer-related ascites. It consists of a plastic or silicon rubber tube fitted with a pressure-activated one-way polypropylene valve that connects the peritoneal space where the fluid is collecting to a large vein located in the neck called the jugular vein. The tube enters the jugular vein and terminates in another large vein called the superior vena cava that returns blood to the heart. Thus, the fluid goes from the abdominal cavity to the venous blood circulatory system and is then eliminated by the kidneys. The function of

the one-way valve is to prevent blood from flowing back into the peritoneal space.

The PVS is inserted under the skin of the chest under local or general anesthesia, depending on the general health condition of the patient.

An alternative option to treat ascites due to cirrhosis is to use a transjugular intrahepatic portosystemic shunt (TIPS). This is also a tube that is passed through the skin of the neck and into the jugular vein but it is pushed all the way through the liver and into the portal vein, which drains into the liver. It thus creates a shunt of blood across the liver in an attempt to reduce pressure and fluid formation.

Preparation

Abdominal computed tomography (CT) scans are used to determine the extent of the ascites. Lab tests are usually performed to determine if the excess abdominal fluid is infected and other **imaging studies** such as ultrasound may be performed to assess the general condition of the veins selected for insertion of the PVS tube. For the operation, the patient is usually injected with a mild sedative and local anesthetic. The surgeon uses a puncture needle to create the opening required for insertion of the PVS device so as to avoid surgical incisions which take longer to heal.

Aftercare

Antibiotics are usually prescribed for approximately four days after surgery. Any **fever** or chills that the patient experiences should be reported to the doctor without delay.

Risks

Complications following PVS insertion are very common and include infection, leakage of fluid, fluid build-up in the lungs, problems with blood coagulation, heart failure and blockage of the PVS device.

Normal results

The PVS insertion is considered successful when the abdominal fluid build-up gradually disappears after the operation.

Abnormal results

The most common complication resulting from PVS insertion is obstruction of the valve or tube, which can be due to a blood clot or to scar tissue forming around the shunt and eventually blocking it. This complication occurs in approximately 60% of cases during the first year of follow-up.

Resources

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Monique Laberge, Ph.D.

PET scan *see* **Positron emission tomography**

Peutz-Jeghers syndrome

Definition

Peutz-Jeghers syndrome (PJS) is a rare familial cancer syndrome that causes intestinal polyps, skin freckling, and an increased risk for cancer.

Description

Peutz-Jeghers syndrome affects both males and females. The characteristic, or pathognomonic, features of PJS are unusual skin freckling and multiple polyps of the small intestine. The skin freckles, which are bluish to brown to black in color, can be found on the lips, inside the mouth, around the eyes, on the hands and feet, and on the genitals. The freckles are called benign hyperpigmented macules and do not become cancerous. The polyps in PJS are called hamartomatous polyps, and are found in the small intestine, small bowel, stomach, colon, and sometimes in the nose or bladder. Hamartomatous polyps are usually benign (not cancerous), but occasionally become malignant (cancerous). Dozens to thousands of hamartomatous polyps may develop. A person with PJS with benign hamartomatous polyps can have abdominal pain, blood in the stool, or complications such as colon obstruction or intussusception (a condition in which one portion of the intestine telescopes into another). Surgery may be required to remove the affected part of the colon. A person with PJS is at increased risk for cancer of the colon, small intestine, stomach and pancreas. Women with PJS are also at increased risk for breast and **cervical cancer**, and a specific type of benign ovarian tumor called SCTAT (sex cord tumors with annular tubules). Men with PJS are also at increased risk for benign testicular tumors.

Diagnosis

The diagnosis of Peutz-Jehgers syndrome can be made clinically in a person with the characteristic

freckles and at least two hamartomatous polyps. A pathologist needs to confirm that the polyps are hamartomatous instead of another type of polyp. If a person has a family history of PJS, the diagnosis can be made in a person who has either freckles or hamartomatous polyps. When someone is the first person in his/her family to be diagnosed with PJS, it is important for all first-degree relatives to be carefully examined for clinical signs of PJS. About half of all persons with PJS will have family members with symptoms of PJS. Symptoms can vary between families and between members of the same family. Some family members may just have freckling and others may have more serious medical problems such as bowel obstruction or cancer diagnosis. The freckles in PJS usually appear in childhood and fade as a person gets older, so it may be necessary to look at childhood photos in an adult who is being examined for signs of PJS.

Risks

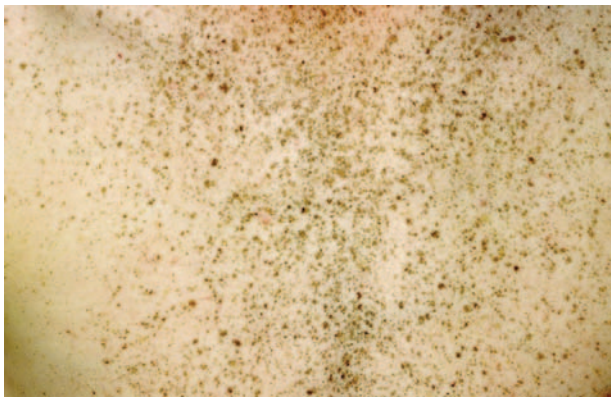
Hamartomatous polyps may be diagnosed from early childhood to later in adulthood. On average, a person with PJS develops polyps by his or her early 20s. The lifetime risk for cancer is greatly increased over the general population, and cancer may occur at an earlier age. Early and regular screening is important to try to detect any cancers at an early stage. The benign ovarian tumors in women with PJS may cause early and irregular menstruation. The benign testicular tumors in men may cause earlier growth spurts and gynecomastia (development of the male breasts).

Causes

PJS is a genetic disease caused by a mutation of a tumor suppressor gene called LBK1 (or STK11) on chromosome 19. The exact function of LBK1 is unknown at this time. PJS is inherited as an autosomal dominant condition, which means that a person with PJS has a 50% chance of passing it on to each of his or her children. Screening and/or **genetic testing** of family members can help sort out who has PJS or who is at risk for developing PJS. Identification of a person with PJS in a family may result in other family members with more mild symptoms being diagnosed, and then receiving appropriate screening and medical care.

Genetic Testing

Fifty percent of people clinically diagnosed with PJS will have a mutation in the LBK1/STK11 gene detected in the lab. The other half will not have a detectable mutation at that time, but may have other PJS-causing genetic mutations discovered in the future.



The unusual skin freckling of Peutz-Jeghers syndrome. Here, the freckles are shown on the chest. *(Custom Medical Stock Photo. Reproduced by permission.)*

In families where a mutation is known, family members can be tested for the same mutation. A person who tests positive for the family mutation will be diagnosed with PJS (even if he or she does not currently show signs of PJS), will need to have the recommended screening evaluations, and is able to pass on the mutation to his or her children. A person who tests negative for a known family mutation will be spared from screening, and his or her children will not be at risk for PJS. When the mutation cannot be found in a family, genetic testing is not useful, and all persons at risk for inheriting PJS will need to have screening for PJS throughout their life span.

Screening and treatment

Regular medical examinations and special screening tests are needed in people with PJS. The age at which screening begins and the frequency of the tests is best determined by a physician familiar with PJS. Screening schedules depend on symptoms and family history. **Colonoscopy**, used to search for polyps in the colon, usually begins in adolescence. X rays and/or upper gastrointestinal endoscopy are used to screen for polyps in the stomach and small intestine. The goal of screening is to remove polyps before they cause symptoms or become cancerous. Surgery may be necessary. Females with PJS need to have annual gynecologic examinations by age 18, and breast **mammography** starting between the ages of 25 and 35. Males with PJS need to have annual testicular examinations. If a person with PJS develops cancer, it is treated as it would be in the general population.

See also Cancer genetics; Familial cancer syndromes.

KEY TERMS

Gynecomastia—Overdevelopment of the mammary glands in males; male breast development.

Intussusception— The folding of one segment of the intestine into another segment of the intestine.

Pathognomonic—Characteristic of a disease; a pattern of symptoms not found in any other condition.

Polyp—A mushroom-like growth that may be a precursor to cancer.

Resources

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Laura L. Stein, M.S., C.G.C

Phenytoin

Definition

Phenytoin is an anticonvulsant, a drug that acts to prevent seizures. In the United States, phenytoin is sold under the brand name Dilantin.

Purpose

Phenytoin helps prevent some types of seizure activity. It is often used to aid in controlling nerve pain associated with some cancers and cancer treatments. Nerve pain causes a burning, tingling sensation. Phenytoin also may be ordered to control a rapid or irregular heart rate. Phenytoin may be given to stop uncontrolled seizures. It may be used during brain surgery to prevent seizure activity. In 2003 a group of researchers in California reported that phenytoin is effective in controlling the acute mania associated with bipolar disorder. Additional uses are under study.

Description

Phenytoin works on areas of the brain to limit electrical discharges and stabilize cellular activity. Like many drugs that control seizures, it also has proven helpful in managing nerve pain.

Recommended dosage

The dose ordered depends on blood levels of the drug determined during routine monitoring. For pain, doctors usually order 200–500 mg per day, either at bedtime or in divided doses. Patients usually start on a low dose. Depending on the patient's response and drug blood levels, the dose may be increased. For seizures, patients are usually started at 100 mg, three times per day. Blood is drawn to check the level of phenytoin in seven to 10 days. The dose is adjusted accordingly. The doctor may prescribe a dose based on an older person's weight. A child's dose also is based on his or her weight.

It is very important that this drug be used exactly as directed. This medication should be taken at the same time every day. Patients should take a missed dose as soon as it is noted. But patients should not take two doses within four hours of each other. This medication should be stored in a dry place, not in the bathroom.

Precautions

Patients should not suddenly stop taking this medication. The abrupt withdrawal of phenytoin could trigger seizures. Patients should not crush or break extended-release drugs. Chewable tablets should be chewed before swallowing. Other pills should be swallowed whole. Older adults may be more prone to adverse effects than younger people. Patients should not change brands without approval of the doctor.

Phenytoin should not be taken by patients who are allergic to this drug. People with slow heart rates, certain other heart conditions, or a flaking, open skin condition also should not take it. Phenytoin may be used cautiously for patients with asthma, allergies, limited kidney or liver function, heart disease, and blood disorders. It also should be used with caution in those with alcoholism, diabetes

mellitus, lupus, poor thyroid function, or porphyria, a rare metabolic disorder. Pregnant women should discuss the risks and benefits of this medication with the doctor. It has been associated with birth defects and possibly cancer in children born to women taking the drug; one study done in 2003 suggests that phenytoin interferes with the normal development of the baby's blood circulation. Expectant mothers who are taking it to prevent seizures should not abruptly stop the drug. Those using it for pain control should discuss its continued use with the doctor. Patients on this drug should not breast feed.

Side effects

Drowsiness is a common side effect of phenytoin. Patients should exercise caution when driving or operating machinery. Alcohol may increase drowsiness. Patients should not consume alcoholic beverages while taking this drug. Other, less frequent effects related to the central nervous system include an unsteady gait, slurred speech, confusion, and dizziness. Patients may experience **depression**, difficulty sleeping, nervousness, irritability, tremors, and numbness. Twitching, headache, mental-health problems including psychotic episodes, and more seizure activity may occur. This medication may also cause **nausea and vomiting**, stomach upset, **diarrhea**, constipation, and swollen gum tissue. Side effects also include a rash, hair loss (**alopecia**) or excessive hair growth, vision changes, uncontrolled eye movements, and inflammation of the surface of the eye. Patients may develop chest pain, swelling, **fever**, increase in weight, enlarged lips, or joint or muscle pain. Patients should practice good dental hygiene to decrease the risk of gum disease. With the doctor's approval, it may be taken with food to decrease stomach upset.

Phenytoin may produce changes in the normal makeup of the blood, including high blood sugar levels and **anemia**. It may trigger disorders of the lymphatic system and cause liver damage. If the liver is not able to properly break down phenytoin, it can produce toxic effects, even at small doses. Doctors typically assess kidney and liver function prior to ordering it. The tests are repeated at regular intervals. Patients should notify the doctor promptly of any side effects. If a skin rash develops, the doctor will instruct the patient how to taper off and stop the drug.

Interactions

Many drugs interact with phenytoin and may increase or decrease its blood levels. Phenytoin may alter the effectiveness of other drugs. The list of interactions is long and varied. Drugs that interfere with phenytoin include anticoagulants (blood thinners), sulfa and other **antibiotics**, antifungal agents, drugs used to treat ulcers, methadone, antidepressants, and disulfiram, which is used to treat alcoholism. It also interacts with **corticosteroids**, estrogen hormones, birth control pills and injections, drugs to treat hypoglycemia, asthma drugs, such other anticonvulsants as carbamazepine, lidocaine, heart medications, Parkinson's disease drugs, anti-inflammatory drugs, narcotic pain relievers, and anticancer drugs. Additionally, taking phenytoin with certain antidepressants may cause seizures in some patients.

Phenytoin has also been reported to interact with certain herbs, including evening primrose (*Oenothera biennis*), gingko (*Gingko biloba*), wormwood (*Artemisia pontica*), and an Ayurvedic preparation known as Shankapulshpi. Patients should always tell their doctors about any herbal preparations they may be taking as well as other prescription medications.

Alcohol ingestion can interfere with maintaining proper blood levels of phenytoin. Patients should not drink alcoholic beverages while taking this medication, as phenytoin can accumulate to toxic levels in the body of noncompliant patients. Antacids and calcium can lower the effectiveness of phenytoin. These drugs should be taken two to three hours apart from phenytoin. Tube feeding may decrease the amount of phenytoin absorbed. Patients should not give tube feedings for two hours before and after taking this drug. Patients should talk to the doctor before taking **folic acid**. It may interfere with this drug.

KEY TERMS

Anticonvulsant—A type of medication given to prevent seizures. Phenytoin is an anticonvulsant.

Bipolar disorder—A mood disorder in which the patient experiences both periods of mania and periods of depression.

Epilepsy—Disorder of the nervous system that causes seizures.

Lymph system—a part of the immune system that includes lymph nodes and tissue.

Mania—The phase of bipolar disorder in which the patient is easily excited, hyperactive, agitated, and unrealistically cheerful. Phenytoin appears to be a useful treatment for mania.

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Pheochromocytoma

Definition

Pheochromocytoma is a tumor of special cells (called chromaffin cells), most often found in the middle of the adrenal gland.

Description

Because pheochromocytomas arise from chromaffin cells, they are occasionally called chromaffin tumors. Most (90%) are benign tumors so they do not spread to other parts of the body. However, these tumors can cause many problems and if they are not treated and can result in death.

Pheochromocytomas can be found anywhere chromaffin cells are found. They may be found in the heart and in the area around the bladder, but most (90%) are found in the adrenal glands. Every individual has two adrenal glands that are located above the kidneys in the back of the abdomen. Each adrenal gland is made up of two parts: the outer part (called the adrenal cortex) and the inner part (called the adrenal medulla). Pheochromocytomas are found in the adrenal medulla. The adrenal medulla normally secretes two substances, or hormones, called norepinephrine and epinephrine. These two substances, when considered together, are known as adrenaline. Adrenaline is released from the adrenal gland, enters the bloodstream and helps to regulate many things in the body including blood pressure and heart rate. Pheochromocytomas cause the adrenal medulla to secrete too much adrenaline, which in turn causes high blood pressure. The high blood pressure usually causes the other symptoms of the disease.

Demographics

Pheochromocytomas are rare tumors. They have been reported in babies as young as 5 days old as well as adults as old as 92 years old. Although they can be found at any time during life, they usually occur in adults between 30-40 years of age. Pheochromocytomas are somewhat more common in women than in men.

Causes and symptoms

The cause of most pheochromocytomas is not known. A small minority (about 10-20%) of pheochromocytomas arise because a person has an inherited susceptibility to them. Inherited pheochromocytomas are associated with four separate syndromes: Multiple Endocrine Neoplasia, type 2A (MEN2A), Multiple Endocrine Neoplasia, type 2B (MEN2B), von Hippel-Lindau disease (VHL), and Neurofibromatosis type 1 (NF1).

Individuals with pheochromocytomas as part of any of these four syndromes usually have other medical conditions, as well. People with MEN2A often have cancer (usually **thyroid cancer**) and other hormonal problems. Individuals with MEN2B can also have cancer and hormonal problems, but also have other abnormal physical features. Both MEN2A and MEN2B are due to genetic alterations or mutations in a gene called RET, found at chromosome 10q11.2. Individuals with VHL often have other benign tumors of the central nervous system and pancreas, and can sometimes have renal cell cancer. This syndrome is caused by a mutation in the VHL gene, found at chromosome 3p25-26. Individuals with NF1 often have neurofibromas (benign tumors of the peripheral nervous system). NF1 is caused by mutations in the NF1 gene, found at chromosome 17q11.

All of these disorders are inherited in an autosomal dominant inheritance pattern. With autosomal dominant inheritance, men and women are equally likely to inherit the syndrome. In addition, children of individuals with the disease are at 50% risk of inheriting it. **Genetic test-**

ing is available for these four syndromes (MEN2A, MEN2B, VHL and NF1) but, due to the complexity, genetic counseling should be considered before testing.

Most people (90%) with pheochromocytoma have hypertension, or high blood pressure. The other symptoms of the disease are extremely variable. These symptoms usually occur in episodes (or attacks) called paroxysms and include:

- headaches
- excess sweating
- racing heart
- rapid breathing
- anxiety/nervousness
- nervous shaking
- pain in the lower chest or upper abdomen
- nausea
- heat intolerance

The episodes can occur as often as 25 times a day or, as infrequently as once every few months. They can last a few minutes, several hours or days. Usually, the attacks occur several times a week and last for about 15 minutes. After the episode is over, the person feels exhausted and fatigued.

Between the attacks, people with pheochromocytoma can experience the following:

- increased sweating
- cold hands and feet
- weight loss
- constipation

Diagnosis

If a pheochromocytoma is suspected, urine and/or a blood tests are usually recommended. A test called "24-hour urinary catacholamines and metanephrines" will be done. This test is designed to look for adrenaline and the break-down products of adrenaline. Since the body gets rid of these hormones in the urine, those testing will need to collect their urine for 24 hours. The laboratory will determine whether or not the levels of hormones are too high. This test is very good at making the diagnosis of pheochromocytoma. Another test called "serum catacholamines" measures the level of adrenaline compounds in the blood. It is not as sensitive as the 24-hour urine test, but can still provide some key information if it shows that the level of adrenaline compounds is too high.

One of the difficulties with these tests is that a person needs to have an attack of symptoms either during the 24-hour urine collection time period or shortly before the blood is drawn for a serum test to ensure the test's accuracy. If a person did not have an episode during that time, the test can be a "false negative." If a doctor suspects the patient has gotten a "false negative" test, additional tests called "pharmacologic tests" can be ordered. During these tests, a specific drug is given to the patient (usually through an IV) and the levels of hormones are monitored from the patient's blood. These types of tests are only done rarely.

Once a person has been diagnosed with a pheochromocytoma, he or she will undergo tests to identify exactly where in the body the tumor is located. The imaging techniques used are usually **computed tomography** scan (CT scan) and magnetic resonance imaging (MRI). A CT scan creates pictures of the interior of the body from computer-analyzed differences in x rays passing through the body. CT scans are performed at a hospital or clinic and take only a few minutes. An MRI is a computerized scanning method that creates pictures of the interior of the body using radio waves and a magnet. An MRI is usually performed at a hospital and takes about 30 minutes.

Treatment team

A pheochromocytoma will usually be treated by an internist (general medical doctor) an anesthesiologist (doctor who administers anesthesia for surgery) and a specialized surgeon (doctor who removes the tumor from the body). If the tumor is found to be malignant, a radiation oncologist (doctor who specializes in radiation treatment for cancer) and medical oncologist (doctor who specializes in **chemotherapy** treatment for cancer) may be consulted.

Clinical staging, treatments and prognosis

Once a pheochromocytoma is found, more tests will be done to see if the tumor is benign (not cancer) or malignant (cancer). If the tumor is malignant, tests will be done to see how far the cancer has spread. There is no accepted staging system for pheochromocytoma; but an observation of the tumor could provide one of these four indications:

- Localized benign pheochromocytoma means that the tumor is found only in one area, is not cancer, and cannot spread to other tissues of the body.
- Regional pheochromocytoma means that the tumor is malignant and has spread to the lymph nodes around the original cancer. Lymph nodes are small structures that are found all over the body that make and store infection-fighting cells.

- Metastatic pheochromocytoma means that the tumor is malignant and has spread to other, more distant parts of the body.
- Recurrent pheochromocytoma means that a malignant tumor that was removed has come back.

Treatment in all cases begins with surgical removal of the tumor. Before surgery, medications such as alpha-adrenergic blockers are given to block the effect of the hormones and normalize blood pressure. These medications are usually started seven to ten days prior to surgery. The surgery of choice is laparoscopic laparotomy, which is a minimally invasive outpatient procedure performed under general or local anesthesia. A small incision is made in the abdomen, the laparoscope is inserted and the tumor is removed. The patient can usually return to normal activities within two weeks. If a laparoscopic laparotomy cannot be done, a traditional laparotomy will be performed. This is a more invasive surgery done under spinal or general anesthesia and requires five to seven days in the hospital. Usually patients are able to return to normal activities after four weeks. After surgery, blood and urine tests will be done to make sure hormone levels return to normal. If the hormone levels are still above normal, it may mean that some tumor tissue was not removed. If not all tumor can be removed (as in malignant pheochromocytoma, for example) drugs will be given to control high blood pressure.

If a pheochromocytoma is malignant, **radiation therapy** and/or chemotherapy may be used. Radiation therapy uses high-energy x rays to kill cancer cells and shrink tumors. Because there is no evidence that radiation therapy is effective in the treatment of malignant pheochromocytoma, it is not often used for treatment. However, it is useful in the treatment of painful bone metastases if the tumor has spread to the bones. Chemotherapy uses drugs to kill cancer cells. Like radiation therapy, it has not been shown to be effective in the treatment of malignant pheochromocytoma. Chemotherapy, therefore, is only used in rare instances.

Untreated pheochromocytoma can be fatal due to complications of the high blood pressure. In the vast majority of cases, when the tumor is surgically removed, pheochromocytoma is cured. In the minority of cases (10%) where pheochromocytoma is malignant, prognosis depends on how far the cancer has spread, and the patient's age and general health. The overall median five-year survival from the initial time of surgery and diagnosis is approximately 43%.

Coping with cancer treatment

If laparascopic laparotomy is done and no further treatment is necessary, patients usually return to normal activity within two weeks. If more extensive surgery is performed, normal activity is delayed for a few weeks and can be emotionally difficult. In rare cases where radiation and/or chemotherapy are needed, coping can be very difficult. Consultation with physicians, nurses, social workers, and psychologists may be beneficial.

KEY TERMS

Adrenal medulla—The central core of the adrenal gland.

Laparoscope—An instrument used to examine body cavities during certain types of surgery; for example, surgeries to remove fibroid tumors, or gall bladders, are often removed through the navel rather than cutting into the body.

Paroxysm—A sudden attack of symptoms.

Prevention

Unfortunately, little is known about environmental and other causes of pheochromocytoma. Some of the tumors are due to inherited predisposition. Because of these factors, pheochromocytoma cannot be prevented.

Special concerns

Pheochromocytoma in children

Pheochromocytoma is rare in children, but occurs most commonly between the ages of 8 and 14 years. Diagnosis of pheochromocytoma can be more difficult at this age, because other **childhood cancers** (e.g. **neuroblastoma**) can also elevate adrenaline compounds in the body. Pheochromocytomas in children are more likely to be bilateral (on both the left and right sides of the body) and outside the adrenal glands. For this reason, transabdominal surgery is usually performed to remove the tumor.

Pheochromocytoma in pregnancy

Although rare, pheochromocytoma in pregnancy can be very dangerous. Because x rays are to be avoided in pregnancy, MRI and/or ultrasound is used to locate the tumor. Alpha-adrenergic blocking agents to reduce blood pressure are given to the woman as soon as the diagnosis is made. If the woman is in the first two trimesters of pregnancy, most often the tumor is removed. In the third trimester, the woman usually remains on alpha-adrenergic blocking agents until a cesarean section can be safely performed.

See also Multiple endocrine neoplasia syndromes; von Recklinghausen's neurofibromatosis.

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Pheresis

Definition

Pheresis is a blood purification process that consists of:

- drawing blood,
- separating red cells, plasma, platelets, and cryoprecipitated antihemophilic factor,
- isolating the blood component needed to diagnose a suspected abnormality or treat a known disease,
- and returning the remaining blood to the donor.

Purpose

Because most of the blood is returned to the donor, pheresis enables an individual to donate more of a specific component. The two main types of pheresis are removal of platelets (plateletpheresis) and removal of plasma (plasmapheresis).

Plateletpheresis

Cancer and cancer treatments can deplete the body's supply of platelets, the colorless particles that stick to the lining of blood vessels and make it possible for blood to clot. Patients who have leukemia or aplastic **anemia**, are receiving **chemotherapy**, or undergoing **bone marrow transplantation** need platelets donated by healthy volunteers to prevent potentially fatal bleeding problems.

Plasmapheresis

Also known as therapeutic plasma exchange, plasmapheresis removes cells from the straw-colored liquid portion of the blood, which contains clotting factors, infection-fighting antibodies, and other proteins. Plasma regulates blood pressure and maintains the body's mineral balance.

Frozen immediately after collection and thawed when needed for transfusion, fresh frozen plasma is sometimes given to control **disseminated intravascular coagulation** (DIC). A particular problem for cancer patients, this rare condition causes large numbers of blood clots to form, then dissolve.

Leukapheresis

Also known as apheresis, leukapheresis may be used to treat certain leukemia and to collect cells for autologous stem cell transplant. Performed before chemotherapy is administered, leukapheresis increases the treatment's impact by reducing the number of cancer cells in the bloodstream and permitting the medication to circulate more freely.

Precautions

The American Red Cross will not accept blood or blood products from anyone who is:

- less than 17 years old
- not in good health
- taking **antibiotics** or insulin
- unable to meet other requirements established to ensure the safety of donated blood

In general, cancer survivors who were treated surgically or with radiation and have been cancer-free for at least five years may donate blood. Because of the remote danger of contracting cancer as the result of a transfusion, blood donations are not accepted from cancer survivors who have been treated with chemotherapy or hormonal therapy or diagnosed with leukemia or **lymphoma**.

The Food and Drug Administration (FDA) requires every blood donor to provide a detailed health history

KEY TERMS

Babesiosis—Infection transmitted by the bite of a tick and characterized by fever, headache, nausea, and muscle pain.

Blood typing—Technique for determining compatibility between donated blood products and transfusion recipients.

Chagas disease—Acute or chronic infection caused by the bite of a tick and characterized by fever, swollen glands, rapid heartbeat, and other symptoms.

QUESTIONS TO ASK THE DOCTOR

- If I make a pheresis donation, can I still donate whole blood?
- What should I do if I change my mind about making a pheresis donation?
- What should I do if I make a pheresis donation and later realize my blood might not be safe?
- How can I find out if I could be a pheresis donor?
- Can I make a pheresis donation for myself, a friend, or a member of my family?

and have a physical examination. All donated blood is tested for babesiosis, bacterial infections, Chagas disease, human immunodeficiency virus (HIV), Lyme disease, malaria, syphilis, and viral hepatitis.

Description

Throughout the procedure, which lasts between 90 minutes and three hours, the pheresis donor relaxes in a specially contoured chair and watches movies or listens to music. A flexible tube inserted into the donor's arm slowly draws blood into a sophisticated machine (centrifuge) which separates the various blood components, collects whichever component is being donated, and returns the remaining blood through a vein in the donor's other arm. Each pheresis donation is typed and designated for a specific patient.

Inserting the needle can cause mild, momentary discomfort. Some pheresis donors feel a slight tingling around the lips and nose, but this sensation disappears as soon as the procedure is completed.

Plasmapheresis and plateletpheresis can be performed in a hospital or blood collection center. Leukapheresis should be performed in a hospital where bone marrow transplantation is frequently performed.

Preparation

Before undergoing pheresis, a donor should get a good night's sleep, eat a well-balanced meal, and drink plenty of caffeine-free liquids. A donor should not take aspirin within 72 hours or ibuprofen within 24 hours before undergoing plateletpheresis, because these medications would make the platelets less beneficial to the patient receiving the transfusion. The donor's physician will determine whether any other medications should be discontinued in preparation for the procedure.

Aftercare

A pheresis donor may feel tired for a few hours and should not plan on driving home after the procedure. Although the donor may resume normal activities right away, heavy lifting or strenuous exercise should be avoided until the following day.

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Photodynamic therapy

Definition

Photodynamic therapy (PDT) is a form of nonsurgical cancer treatment available since the early 1990s that

combines a photosensitizing medication with exposure to a laser or other specific light wavelength to kill cancer cells. It can be used before or after surgery and other forms of cancer treatment. In some cases, PDT can even be administered during surgery to kill any cancer cells that were not removed by excision.

Purpose

Photodynamic therapy is still evolving, both in terms of the types of cancer it is approved to treat and the specific drugs that are used. PDT with a drug called **porfimer sodium** (Photofrin) was first approved as a treatment for **esophageal cancer** in 1995. The Food and Drug Administration (FDA) then extended its approval of this drug to cover **non-small cell lung cancer** in 1998. As of the early 2000s, the FDA has also approved porfimer sodium for the treatment of tumors located in the bronchi of the lungs and for palliative treatment of advanced cancers of the esophagus. Some cancer centers in the United States administer PDT with porfimer sodium for the treatment of certain types of skin cancer (squamous cell **carcinoma**, **basal cell carcinoma**, and Bowen's disease), recurrences of **breast cancer** following **mastectomy**, colorectal cancer, and cancers of the vulva and cervix, but these applications of PDT are still considered experimental as of early 2005.

In December 1999, the FDA approved a compound called aminolevulinic acid (ALA or Levulan Kerastick) for the treatment of actinic keratosis, a precancerous skin disorder caused by sun exposure. Experimental uses of ALA, as of the early 2000s, include treatment of **mycosis fungoides** and cancerous tumors on the surface of the skin.

Porfimer sodium and ALA are the only photosensitizing agents approved by the FDA for use in the United States as of 2005; however, several newer drugs for PDT are being tested in cancer centers in the United States and Europe. The most important of these will be described below.

In addition to cancer therapy, PDT is used to treat such conditions as wet macular degeneration, an eye disorder that can lead to blindness, as well as such benign skin conditions as psoriasis, acne, and skin disorders caused by the **human papilloma virus**. In addition, PDT is under investigation as a possible treatment for certain forms of coronary artery disease.

Precautions

Precautions for porfimer sodium (Photofrin):

- Porfimer sodium cannot be used in patients who are allergic to hematoporphyrin, a blood pigment used to make the drug.
- It cannot be used in pregnant or nursing women because its safety during pregnancy or lactation has not been established.
- It cannot be used to treat children.
- Lung tumors treated with Photofrin must be located in an airway where the doctor can reach them with a brochoscope.
- Photofrin cannot be used to treat tumors in the esophagus or bronchi that are beginning to break into the patient's windpipe or a major blood vessel. The drug should also be used cautiously in treating bronchial tumors that could block the airway if they develop inflammation following PDT.
- Patients who are receiving radiotherapy should not have PDT with porfimer sodium until 4 weeks after their last radiation treatment. They should also not be treated with radiotherapy until 2–4 weeks after a PDT treatment.

Precautions for aminolevulinic acid (ALA):

- Patients being treated with ALA must protect their skin from exposure to sunlight or bright indoor light in the short time period between application of the drug to the skin and the PDT treatment.
- ALA should be used cautiously in pregnant women or nursing mothers.
- If a second treatment is necessary, it should not be done before eight weeks after the first treatment.

Description

How PDT works

Photodynamic therapy is based on a series of chemical reactions involving a specific wavelength of visible light, a photosensitizing drug, and oxygen. There is no standard wavelength of light, light source, exposure period, or method of administering the medication that covers all forms of PDT. Most photosensitizing drugs are given intravenously, but some are applied to the skin or taken by mouth. Photosensitizers given by injection are activated by light in the red portion of the visible light spectrum, around 630–700 nanometers (nm; a nanometer is a measure of length, one billionth of a meter), while those applied to the skin are usually activated by blue light.

In general, cancerous tumors inside the body need more concentrated doses of light than abnormal growths on the body surface. Lasers are usually used to deliver highly concentrated light at one specific wavelength, while light sources that provide a larger area of illumination, such as light-emitting diodes (LEDs), are more efficient for treating skin tumors.

In contrast to their uses in surgery, lasers are not used in PDT to remove tissue or seal blood vessels with heat; rather they are used to start a chemical reaction. As a result, they do not become hot enough to burn tissue. The burning or stinging sensation that some patients experience during PDT is caused by the release of oxygen stimulating nearby nerve endings rather than heat from the laser itself.

Lasers can be attached to fiberoptics for treating tumors inside the body. Fiberoptics are thin strands of plastic or glass with special optical properties that can be threaded through a bronchoscope or endoscope, which are special tubes that allow the doctor to see into the patient's lungs or esophagus. Light from the laser is then transmitted along the special fibers to the tumor, thus allowing the doctor to activate the photosensitizing medication in a very small area of tissue without damaging normal tissue nearby.

PDT is a two-step form of therapy. First, the photosensitizing medication is injected into a vein or applied to the skin several days or hours before the scheduled treatment. The drug is absorbed by all body tissues but remains in cancer cells longer than in normal cells because the cancer cells are multiplying faster. After the medication has had time to collect in the malignant cells, the doctor directs a light source of the proper wavelength on the targeted area. When the light source strikes tissue containing the photosensitizing medication in the presence of oxygen, the medication is activated and produces free radicals and a highly reactive form of oxygen called singlet oxygen. The free radicals and singlet oxygen interact with the cell membranes of the cancer cells to destroy the energy-producing structures inside the cancer cells. In addition to killing the cancer cells directly, PDT works by closing blood vessels inside the tumor, thereby shutting off its supply of nutrients, and by stimulating the immune system to produce interleukins (nonantibody proteins) and other substances that attack the cancer.

Photosensitizing drugs

PORFIMER SODIUM Porfimer sodium, or Photofrin, was the first medication used for PDT. It is a purified derivative of hematoporphyrin, a dark reddish-purple pigment found in blood. Photofrin is activated by red light at a wavelength of 630 nm; one disadvantage of this short wavelength is that it cannot penetrate tissue deeper than about a third of an inch, thus making Photofrin unsuitable for treating tumors that lie deep beneath the surface. The light used to activate Photofrin is usually generated by a laser.

Porfimer sodium has several other disadvantages for PDT: It is a complex chemical mixture that tends to break down over time; it has limited ability to penetrate tissue; and it takes 4–6 weeks to be cleared from the skin, thus leaving patients susceptible to a photosensitivity reaction for a long period of time after their PDT treatment. A photosensitivity reaction occurs when sensitized skin is exposed to sunlight or other bright light and is characterized by redness, swelling, and blistering of the exposed skin. As a result of Photofrin's disadvantages, researchers have been studying other photosensitizers with the following characteristics:

- They are single compounds rather than mixtures of chemicals.
- They are more effective in absorbing the red region of the visible light spectrum.
- They are more selective in targeting malignant tissue.
- They are more efficient in generating singlet oxygen.

AMINOLEVULINIC ACID Aminolevulinic acid, or ALA, is a short-lived photosensitizer that is applied to the skin as a 5–20% oil-in-water mixture. It is activated by either a special blue light illuminator or by light at 630–635 nm.

SECOND-GENERATION PHOTOSENSITIZERS Newer photosensitizing agents that are being used in **clinical trials** as of 2005 include:

- HPPH (2-[1-hexyloethyl]-2-devinyl-pyropheophorbide-a; brand name Photochlor). HPPH is a photosensitizer that is activated by light more efficiently than Photofrin. In addition, patients treated with HPPH do not have the long-term photosensitivity reactions associated with Photofrin. HPPH has been used experimentally since 2003 at the Roswell Park Cancer Institute in Buffalo, New York, to treat esophageal cancer, Barrett's esophagus, basal cell carcinoma, and recurrent breast cancer following mastectomy. It is also undergoing clinical trials in schools of veterinary medicine as a possible treatment for cancers in cats and dogs. Like Photofrin, HPPH is given intravenously.
- Verteporfin (also known as BPD-MA [benzoporphyrin derivative monoacid ring A]; brand name Visudyne). Verteporfin is a second-generation photosensitizer used primarily to treat eye disorders, including age-related macular degeneration, other abnormal formations of blood vessels within the eye, and histoplasmosis (an eye infection caused by a fungus). Verteporfin is also being investigated as a possible treatment for skin cancer and psoriasis.
- Temoporfin (Meta-tetra hydroxyphenyl chlorin; brand name Foscan). Temoporfin is a chlorin-type photosensitizer developed in the United Kingdom. It was approved by the European Union in 2001 for the treatment of **head and neck cancers** and certain types of

lung cancer, but is categorized as an orphan drug in the United States. The FDA lists temoporfin as an orphan drug for the palliative treatment of inoperable head and neck cancers.

- Motexafin lutetium (brand name Lu-Tex). Lu-Tex is an injectable dye that has been used in clinical trials to treat malignant **melanoma**. It has a high degree of selectivity for cancer cells. It also shows promise as a treatment for recurrent breast cancer and atherosclerosis.

Clinical trials

Although the National Cancer Institute (NCI) is not conducting trials of new PDT drugs as of 2005, there are several cancer centers in the United States and Canada that are investigating Photochlor and other second-generation photosensitizers.

Preparation

PDT for skin conditions

A patient receiving PDT for skin cancer or a precancerous skin disorder will have ALA applied to the affected area 3–6 hours before the scheduled treatment. The skin may or may not be covered with a dressing. The patient does not need to fast or make any other special preparations. If the affected area of skin is on the face, the patient may be given goggles to wear to protect the eyes from the blue light used to activate the drug.

PDT for internal cancers

The photosensitizing agents used for PDT or palliative treatment of esophageal or lung cancers are given by injection, usually 2–3 days before treatment. The patient may return home after the injection, but must avoid sunlight and bright light indoors before the light treatment. The patient does not need to fast or discontinue other medications, but should cover the windows and skylights in their home before receiving the light treatment to prevent exposure to bright light after returning home.

Patients undergoing PDT for esophageal or lung cancers are given a local or general anesthetic before the doctor inserts the bronchoscope or endoscope. They may also be given a mild tranquilizer to relieve anxiety.

Aftercare

Aftercare following PDT with porfimer sodium involves 4–6 weeks of protection from sunlight and other sources of bright light, including tanning lamps or the examination lamps found in doctors' and dentists' offices. During this period, the patient should wear dark glasses; long-sleeved shirts of light-colored, and tightly woven fabric long pants or slacks; and a wide-brimmed hat to protect the skin and eyes outdoors for at least 30 days after treatment. Sunscreen creams and lotions do not provide enough protection. It is best to run necessary errands after sundown or ask someone else in the household to drive the car. Women should not use helmet-type hair dryers or hand-held dryers on a high setting, as the drug remains in the scalp for several weeks and may cause burns if exposed to high heat. Exposure to low levels of indoor light is necessary, however, in order to break down the Photofrin remaining in the skin. After 30 days, the doctor will give the patient instructions on testing the skin for any remaining sensitivity to light.

Patients who have received PDT for cancers in the lining of the bronchi must return two days after the treatment for a follow-up **bronchoscopy**, in which the doctor will remove dead tumor cells and other pieces of tissue from the treated area. This follow-up procedure is necessary to prevent inflammation and possible blockage of the patient's airway. Treated tumor sites require between 4 and 8 weeks for complete healing.

Patients who receive PDT with ALA do not need to take special precautions regarding sun exposure after treatment because the drug is short-lived. The treated skin will usually form a crust or scale for several days before healing completely.

Risks

Porfimer sodium

Risks of PDT with porfimer sodium include photosensitivity reactions if the patient fails to observe the guidelines for aftercare; chest pain or a burning sensation in the chest or throat; difficulty swallowing; **itching**; the formation of ulcers or scar tissue; and discomfort in the eyes when exposed to sunlight, bright lights, or car headlights. Breast cancer and lung cancer patients who have severe chest pain after PDT can be given medications to control the pain.

Aminolevulinic acid

Some patients experience a stinging or burning sensation in the skin during the blue light treatment, but this usually goes away as soon as the light is turned off. Some patients also report temporary swelling or redness of the skin in the treated areas, or minor changes in the pigmentation of their skin.

Normal results

Normal results of PDT of the esophagus or the lining of the bronchi are shrinkage of the tumor and

KEY TERMS

Actinic keratosis (plural, keratoses)—A type of precancerous skin growth with a scaly or bumpy surface caused by overexposure to the sun.

Barrett's esophagus—A precancerous condition of the esophagus that may develop as a complication of gastroesophageal reflux disease (GERD).

Bronchi (singular, bronchus)—The larger air passages inside the lungs.

Fiberoptics—Bundles of specially treated glass or plastic fibers that intensify light from a light source by internal reflection. Fiberoptics can be attached to lasers for use in PDT.

Free radicals—Molecules that contain at least one unpaired electron. They are highly reactive and can destroy cells by disrupting their normal biological processes. Free radicals are released during PDT and help to kill tumor cells.

Hematoporphyrin—A dark reddish-purple pigment found in blood. A purified form of hematoporphyrin is used to make porfimer sodium.

Nanometer—A measurement of length equal to 10^{-9} meters, or one billionth of a meter. It is used as a unit of measurement for light waves.

Orphan drug—A drug that treats a rare disease—"rare disease" being defined by the Food and Drug Association as one affecting fewer than 200,000 Americans. The category of orphan drug includes experimental as well as approved medications. Some photosensitizing drugs used in Europe are considered orphan drugs in the United States.

Palliative—Referring to treatment used to relieve the symptoms of a disease or disorder rather than to cure it.

Singlet oxygen—A highly reactive form of the oxygen molecule (O_2) formed during PDT that helps to destroy cancer cells by attacking their cell membranes.

destruction of cancer cells. Normal results of palliative treatment for cancer of the esophagus are sufficient shrinkage of the tumor to allow the patient to swallow again.

Normal results for PDT of the skin include shrinkage and destruction of the tumor, although large skin tumors may require a second treatment for complete removal.

QUESTIONS TO ASK YOUR DOCTOR

- Is photodynamic therapy a possible treatment option for my cancer?
- Are you experienced in treating patients with PDT?
- Should I consider enrolling in a clinical trial of a new PDT drug?

Abnormal results

Abnormal results include allergic reactions to the photosensitizing medication or failure of the tumor to respond to PDT.

See also Esophageal cancer; Porfimer sodium.

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Rebecca Frey, PhD

PICC lines *see* **Vascular access**

Pilocarpine

Definition

Pilocarpine is a medicine used to treat **xerostomia**, or dryness of the mouth, caused by a decrease in saliva production following radiation or due to **Sjögren's syndrome**, a disorder of the immune system characterized by the failure of the exocrine glands. Pilocarpine is also known as pilocarpine hydrochloride or Salagen.

Purpose

Pilocarpine is used to treat side effects arising from radiation treatment for **head and neck cancers**. It alleviates dryness of the mouth and throat and aids in chewing, tasting, and swallowing. It may also be given to treat dryness of the eyes resulting from cancer treatment.

Pilocarpine is also used in the form of eye drops or eye gel to treat glaucoma; it works by lowering the pressure of the fluid inside the eye.

Description

Pilocarpine is a naturally occurring substance found in the leaflets of *Pilocarpus jaborandi*, a South American shrub.

Pilocarpine works by stimulating the function of the exocrine glands, including the glands that produce saliva, sweat, tears, and digestive secretions. It also stimulates smooth muscles, such as those found in the bronchus, gallbladder, bile ducts, and intestinal and urinary tracts.

Pilocarpine was approved by the United States Food and Drug Administration as a sialogogue, or medication to increase the flow of saliva, in 1994. Pilocarpine was effective in relieving xerostomia symptoms after twelve weeks in over half the patients studied; however, the medication may not work for everyone.

Recommended dosage

Pilocarpine is taken orally. It is available in round white tablets containing 5 mg. Different patients may require different dosages of the drug. The usual dose for adults is five milligrams taken three times a day. If necessary, the physician may increase the dosage to 10 mg, three times a day. Since increasing the dose increases the likelihood of side effects, the lowest dose that is effective should be used for treatment.

Pilocarpine begins to act 20 minutes after ingestion. It will continue to act for three to five hours, with the maximum effect taking place one hour after ingestion. Twelve weeks of regular use may be required for an improvement of symptoms.

If a dose is missed, it should be taken as soon as possible; however, if it is almost time for the next dose, only the next dose should be taken.

Precautions

Patients may wish to take this medication with a meal to avoid stomach upset; however, pilocarpine will have reduced effectiveness if it is taken with a meal that is high in fat. Patients should drink plenty of water to avoid dehydration due to increased sweating. Alcohol and antihistamines should not be used while taking pilocarpine. Due to the possibility of visual disturbances or dizziness, people using this medication should avoid driving or operating machinery, particularly at night. Patients should continue to see a dentist regularly during treatment even though symptoms may be improved, since xerostomia may increase the likelihood of tooth decay and other dental problems.

Studies have not been done to test the safety of pilocarpine use in pregnant or nursing women; very high doses of the drug may cause birth defects in animals. Studies have also not been done to test the use of pilocarpine by children.

Pilocarpine should not be taken by people who are sensitive to it or who have uncontrolled asthma, or such eye problems as inflammation of the iris or angle-closure glaucoma. It should be used with caution by people with breathing problems, gallbladder disease, kidney problems, peptic ulcer, psychological disturbances, retinal disease, or heart or blood vessel disease.

Side effects

The most common side effect of pilocarpine use is increased sweating. Other less common side effects are as follows: **nausea and vomiting**, irritated nose, chills, flushing, frequent urination, dizziness, weakness, headache, difficulty with digestion, increased tear production, **diarrhea**, bloating, abdominal pain, and visual problems.

Symptoms of overdose include irregular heartbeat, chest pain, fainting, confusion, stomach cramps or pain, and trouble breathing. Unusually severe or continuing side effects such as diarrhea, headache, weakness, trembling, visual difficulties, nausea, and vomiting may also indicate overdose.

Interactions

Pilocarpine may interact with other medications, reducing or increasing their effects or, sometimes, increasing the side effects of the other medications. Pilocarpine may also be less effective as a result of interaction with other medications. The following drugs may cause interactions:

- amantadine
- anticholinergics
- antidepressants
- antidyskinetics
- antihistamines
- antimyasthenics
- antipsychotics
- beta-adrenergic blocking agents
- bethanecol
- buclizine
- carbamazepine
- cyclizine
- cyclobenzaprine
- disopyramide
- flavoxate
- glaucoma medications
- ipratropium
- meclizine
- methylphenidate
- orphenadrine
- oxybutynin
- physostigmine
- procainamide
- promethazine
- quinidine

Pilocarpine may also interact with alcohol, cocaine, and marijuana.

KEY TERMS

Exocrine—Referring to a gland that secretes outward by way of a duct.

Sialogogue—A medication given to increase the flow of saliva. Pilocarpine may be used as a sialogogue.

Xerostomia—The medical term for dry mouth.

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Pineoblastoma

Definition

A pineoblastoma is an aggressive primary brain tumor that develops in the pineal body (sometimes called

the epiphysis cerebri or pineal gland), which is a small cone-shaped organ located in the midbrain. The pineal body secretes melatonin, a hormone that regulates moods and the sleep-wake cycle in humans. Pineoblastomas are also known as pinealoblastomas.

Description

Pineoblastomas are rapidly growing tumors, and thereby distinguished from pineocytomas, which grow relatively slowly. They are defined by the World Health Organization (WHO) as primitive neuroectodermal tumors (PNETs) in the pineal gland; the word *primitive* in this context means that these tumors are composed of cells that have not yet separated into more specialized types of cells. The word *neuroectodermal* means that these tumors develop out of a layer of cells in the embryo that eventually gives rise to the baby's nervous system.

Pineoblastomas are considered highly malignant. They may invade nearby areas of brain tissue as well as spread into the cerebrospinal fluid, although they rarely metastasize to other parts of the body. In addition, pineoblastomas sometimes cause bleeding into the ventricles of the brain. The child's radiologist may be able to see areas of dying tissue in the brain when **imaging studies** are performed.

Demographics

Pineoblastomas are extremely rare, accounting for only 0.5–2 percent of childhood tumors of the central nervous system (CNS). About 2200 children below the age of 15 are diagnosed with malignant tumors of the brain and spinal cord each year in the United States; between 10 and 40 of these children will be diagnosed with pineoblastomas.

It is difficult to evaluate the statistical significance of racial or gender differences in such a small group; however, the available evidence from American cancer registries suggests that these cancers occur more frequently in Caucasian children than in African Americans, and more frequently in males than in females.

Pineoblastomas occur almost exclusively in younger children, with very few cases reported in adolescents or adults. The slower-growing pineocytomas, by contrast, are most likely to develop in adults between the ages of 25 and 35.

Causes and symptoms

The cause of pineoblastomas is unknown, as of early 2005, but may be associated with gene mutations. A group of British radiologists reported in 2004 that the chances of survival in children diagnosed with pineoblastoma who had inherited a mutation of the **retinoblastoma** (RB) gene are much lower than the chances of children who did not inherit the RB mutation. The researchers suggested that this mutation may cause pineoblastomas as well as reduce or inhibit their response to therapy.

The symptoms of a pineoblastoma result from blockage of the flow of cerebrospinal fluid and increased pressure on the brain. Depending on the size of the tumor, symptoms may include the following:

- headache
- double vision
- **nausea and vomiting**
- weakness or loss of sensation on one side of the body
- seizures
- developmental delays or failure to thrive (in younger children)
- lowered energy level or unusual need for sleep
- personality changes
- unexplained changes in weight or appetite

Parents should note, however, that these symptoms are not unique to pineoblastomas; they may be produced by other types of brain tumors, head trauma, meningitis, migraine headaches, or several other medical conditions. In any event, a child with these symptoms should be seen by a doctor at once.

Diagnosis

The diagnosis of a pineoblastoma begins with a review of the child's medical history and a thorough physical examination. The child may be given several vision tests if he or she is seeing double or having other visual disturbances. The child's doctor will then order both laboratory tests and imaging studies. The laboratory tests are done to rule out such diseases as meningitis and to see whether the child's liver and other organs are functioning normally. The imaging studies are performed to determine the extent of the cancer and to assign the child to a risk group.

Unless surgical removal of the tumor is considered too risky, a neurosurgeon will perform what is known as an open **biopsy** to confirm the diagnosis of pineoblastoma. He or she will remove a small piece of the tumor for examination by a pathologist.

Laboratory tests

Standard laboratory tests for children with brain tumors include a complete blood count (CBC), electrolyte analysis, tests of kidney, liver, and thyroid function,

and tests that determine whether the child has been recently exposed to certain viruses. In addition, a **lumbar puncture** will be performed to look for cancer cells in the child's spinal fluid.

Imaging tests

Imaging tests for pineoblastomas include the following:

- Magnetic resonance imaging (MRIs).
- Computed tomography (CT) scan. Doctors usually order MRIs and CT scans that cover the full length of the spinal column as well as the brain, because pineoblastomas are more likely than other PNETs to spread into the cerebrospinal fluid.
- Chest x ray.
- Bone scan. This test is necessary to determine whether the tumor has spread beyond the central nervous system.

Treatment team

Since the 1960s, most children diagnosed with brain tumors have been treated in specialized children's cancer centers. A child with pineoblastoma will usually have a pediatric oncologist as his or her primary doctor, along with one or more specialists. These specialists may include a neurosurgeon, pathologist, neuroradiologist, radiation oncologist, medical oncologist, endocrinologist, nutritionist, physical therapit or rehabilitation specialist, and psychologist or psychiatrist. The team will also include social workers, clergy, and other professionals to help the parents cope with the stresses of their child's illness and treatments.

Clinical staging, treatments, and prognosis

Staging

Pineoblastomas are not staged in the same way as cancers elsewhere in the body. Instead, children with these tumors are divided as of the early 2000s into two risk groups, average risk and poor risk. Assignment to these groups is based on the following factors:

- child's age
- size and location of the tumor
- whether the tumor has spread to other parts of the central nervous system
- whether the tumor has spread beyond the CNS to other parts of the body

Average-risk children are those older than three years, with most or all of the tumor removed by surgery and no evidence that the cancer has spread beyond the pineal body. Poor-risk children are those who are younger than three years, whose cancer was located near the center of the brain or could not be removed completely by surgery, and whose cancer has spread to or beyond other parts of the CNS. The risk of recurrence is higher for children in the poor risk group.

Treatments

Treatments for pineoblastoma depend on the child's age and his or her risk group. Children younger than three years are not usually given **radiation therapy** because it can affect growth and normal brain development; they are usually treated with surgery to remove as much of the tumor as possible, followed by **chemotherapy** if they are considered poor-risk patients. The drugs most commonly used to treat PNETs include **lomustine**, **cisplatin**, **carboplatin**, and **vincristine**.

In addition to removing the tumor, the surgeon may also place a shunt to reduce pressure on the child's brain if the tumor is blocking the flow of cerebrospinal fluid. The shunt is a plastic tube with one end placed within the third ventricle of the brain. The rest of the shunt is routed under the skin of the head, neck, and chest with the other end placed in the abdomen or near the heart. Shunts are used very conservatively in children with pineoblastomas, however, because there have been reports of these tumors spreading into the abdomen via the shunt.

Children three years and older are treated with surgery first, followed by radiation treatment of the entire brain and spinal cord. Those considered poor risks may also be given chemotherapy. Recurrent pineoblastomas are treated with further surgery and an additional course of chemotherapy.

Treatments for pineoblastoma that are considered experimental as of 2005 include the following:

- Gamma knife surgery (GKS). One group of neurosurgeons in Florida has reported good results in treating children with tumors in the pineal body with GKS. The advantages of GKS include more complete tumor removal and quicker recovery for the patient.
- Gene therapy.
- High-dose chemotherapy.
- **Photodynamic therapy**.
- Stem cell and **bone marrow transplantation**.
- Newer drugs: **Irinotecan**, tipifarnib, lapatinib, ixabepilone, cilengitide, and tariquidar.

Prognosis

The prognosis for children with pineoblastomas depends largely on their risk group. In general, however,

these tumors have a poorer prognosis than other types of brain tumors, in part because of the difficulty of removing the complete tumor due to the location of the pineal body deep within the brain. The overall five-year survival rate of children with pineoblastoma is reported to be 50–60 percent, but is much lower in children younger than three years and in older children who do not respond to radiation therapy.

Recurrent pineoblastomas are almost always fatal; there are no effective therapies for recurrent PNETs, as of the early 2000s.

Alternative and complementary therapies

Some complementary therapies that are reported to help children with pineoblastomas include pet therapy, humor therapy, and music therapy. All of these can be pleasurable for the child as well as relaxing. Ginger or peppermint may help to relieve the nausea and vomiting associated with chemotherapy.

Coping with cancer treatment

Children can be given additional medications to treat nausea and other side effects of chemotherapy. With regard to homesickness and other emotional reactions to being away from home, children's cancer centers have social workers and child psychologists who can educate the child's family about the cancer as well as help the child deal with separation issues.

The side effects of radiation therapy in children with brain tumors may include the formation of dead tissue at the site of the tumor. This formation is known as radiation necrosis. It occurs in about 5 percent of children who receive radiation therapy and may require surgical removal. Radiation necrosis, however, is not as serious as recurrence of the tumor.

Children who have difficulty speaking after brain surgery, or who experience physical weakness, difficulty walking, visual impairment, or other sensory problems, are given physical therapy and/or speech therapy on either an inpatient or outpatient basis.

Clinical trials

Because pineoblastomas are so rare, the American Cancer Society recommends that children diagnosed with these tumors be enrolled in an appropriate clinical trial. As of early 2005, there are about 30 **clinical trials** in the United States for children with pineoblastomas and other PNETs. Some of these trials involve gene testing to improve diagnosis of children with brain tumors, while others are exploring various combinations of chemotherapy (including new agents), photodynamic therapy, stem cell transplantation, and bone marrow transplantation as treatments for pineoblastomas.

KEY TERMS

Blastoma—An abnormal growth of embryonic cells. A pineoblastoma is a blastoma that develops in the pineal body.

Endocrinologist—A doctor who specializes in diagnosing and treating disorders that affect the balance of hormones in the body or the organs that produce these hormones.

Melatonin—A hormone that regulates moods and the sleep-wake cycle in humans. It is produced by the pineal body.

Pineal body—A small cone-shaped endocrine gland attached to the roof of the third ventricle of the brain. The pineal body, which is also known as the pineal gland or epiphysis, secretes melatonin.

Pineocytoma—A slower-growing tumor of the pineal body found more commonly in adults.

Primary brain tumor—A tumor that starts in the brain, as distinct from a metastatic tumor that begins elsewhere in the body and spreads to the brain. A pineoblastoma is one type of primary brain tumor.

Primitive—Simple or undifferentiated. Pineoblastomas are classified as primitive tumors because they arise from cells that have not yet separated into groups of more specialized cells.

Shunt—A tube inserted by a surgeon to relieve pressure on the brain from blocked cerebrospinal fluid. The tube allows the fluid to bypass the tumor that is blocking its flow.

Ventricle—One of the small cavities located within the brain. The pineal body is attached to the roof of the third ventricle.

Prevention

There is no way to prevent pineoblastomas as of the early 2000s because their cause is still unknown.

Special concerns

Children diagnosed with pineoblastomas, like children with other long-term illnesses, may develop emotional problems in reaction to restrictions on their activities, uncomfortable treatments, or being treated in a cancer center away from home. These children may

QUESTIONS TO ASK YOUR DOCTOR

- Which risk group has my child been assigned to?
- What treatments would you recommend for a child in that group, and why would you recommend them?
- Is my child eligible for any current clinical trials for children with pineoblastoma?
- Would you recommend any of the treatments currently considered experimental?
- What is my child's life expectancy? What can I do to make the remaining time as pain-free and enjoyable as possible?

withdraw from others, become angry or bitter, or feel inappropriately guilty about their illness. It is important to reassure the child that he or she did not cause the cancer or deserve it as a punishment for being "bad." Parents may benefit from consulting a child psychiatrist about these and other emotional problems.

Another special concern is the task of explaining the child's illness and treatments to other family members and friends in ways that they can understand. Members of the child's treatment team can be helpful in providing simplified descriptions for siblings or schoolmates.

A third area of concern with **childhood cancers** is the parents' relationships with their other children and with each other. Siblings may resent the amount of time and attention given to the child with cancer, or they may fear that they too will develop a brain tumor. Support groups for families of children with cancer can help by sharing strategies for coping with these problems as well as allowing members to express anxiety and other painful feelings in a safe setting.

See also Brain tumors; Supratentorial primitive neuroectodermal tumors.

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ORGANIZATIONS

American Academy of Child and Adolescent Psychiatry. 3615 Wisconsin Avenue, NW, Washington, DC 20016-3007. (202) 966-7300. Fax: (202) 966-2891. <http://www.aacap.org.>.

American Brain Tumor Association (ABTA). 2720 River Road, Des Plaines, IL 60018. (800) 886-2282 or (847) 827-9910. <http://www.abta.org>. This independent nonprofit association supports research as well as providing patient and family education materials.

CureSearch Children's Oncology Group (COG) Research Operations Center. 440 East Huntington Drive, P. O. Box 60012, Arcadia, CA 91066-6012. CureSearch is a joint effort of two organizations, the Children's Oncology Group (COG) and the National Childhood Cancer Foundation (NCCF). The COG conducts research and clinical trials while the NCCF conducts fundraising and advocacy initiatives.

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Rebecca Frey, PhD

Pituitary tumors

Definition

Pituitary tumors are abnormal growths in the pituitary gland.

Description

Located in the brain, the pituitary gland is often referred to as the "master gland" of the body. This is because it makes and releases (secretes) at least nine distinct hormones (including oxytocin, antidiuretic hormone [ADH], prolactin, thyroid-stimulating hormone [TSH], adrenocorticotropic hormone [ACTH], follicle-stimulating hormone [FSH], luteinizing hormone [LH], and human growth hormone [HGH]) that regulate the activities of several other endocrine glands and influence a number of physiological processes including growth, sexual development and functioning, and the fluid balance of the body. The pituitary is divided into two parts: front (anterior) and rear (posterior). Each half of the pituitary gland secretes specific hormones. Tumors in the anterior part are common and are usually noncancerous (benign). Tumors rarely develop in the posterior portion. Between 10% and 15% of all tumors in the skull are pituitary tumors, which makes them the third most common type of brain tumor.

Virtually all pituitary tumors arise from a single cell which, for unknown reasons, has grown out of control. Tumors that have originated from a single cell are called monoclonal. Some tumors secrete hormones normally made by the pituitary gland. Because the tumor cells are uncontrolled, they secrete large amounts of hormones. As a result, hormone imbalance occurs. The symptoms caused by the hormone imbalance are often the first sign of a pituitary tumor.

There are several different types of pituitary tumors. Pituitary adenomas (adenomas are tumors that grow from gland tissues) are the most common type. Most pituitary adenomas are benign, although they may spread to nearby tissues. Pituitary adenomas can be further classified based on which, if any, hormones are secreted by the tumor. Thirty-five percent of pituitary adenomas do not secrete hormones, 27% secrete prolactin (prolactinomas), and 21% secrete growth hormone. The remaining pituitary adenomas secrete sex hormones (6%), thyroid hormones (1%), or adrenal (adrenocorticotropic) hormones (8%). Plurihormonal adenomas secrete more than one type of hormone. Tumors that secrete adrenocorticotropic hormone cause **Cushing's syndrome** and Nelson's syndrome.

Craniopharyngiomas are benign tumors that originate in tissues next to the pituitary gland. Technically speaking, they are not pituitary tumors although they affect the pituitary gland. They are extremely difficult to remove and radiation does not stop craniopharyngiomas from spreading throughout the pituitary gland. Craniopharyngiomas account for less than 5% of all brain tumors.

Pituitary **carcinoma** is a very rare condition. Fewer than 100 cases have ever been reported. It is usually diagnosed when a pituitary tumor, which was believed to be an **adenoma**, spreads (metastasizes) to distant organs. These pituitary tumors may or may not release hormones. Because pituitary carcinoma is often diagnosed late, it has a high death rate.

Demographics

Pituitary tumors occur more frequently in women than in men. They usually develop between the ages of 30 and 40. Half of all craniopharyngiomas occur in children, with symptoms most often appearing between the ages of five and ten.

Causes and symptoms

The cause of pituitary tumors is not known. Most pituitary tumors presumably result from changes to the DNA of one cell, leading to uncontrolled cell growth. The genetic defects, multiple endocrine neoplasia syndrome type I (MEN I or Wermer's syndrome), McCune-Albright syndrome, and the Carney complex, are associated with pituitary tumors. However, these defects account for only a small percentage of the cases of pituitary tumors. Also, a pituitary tumor may result from the spread (**metastasis**) of cancer from another site. **Breast cancer** in women and lung cancer in men are the most common cancers to spread to the pituitary gland. Other cancers that spread to the pituitary gland include kidney cancer, **prostate cancer**, **melanoma**, and **gastrointestinal cancers**.

Symptoms related to tumor location, size, and pressure on neighboring structures include:

- persistent headache on one or both sides, or in the center of the forehead
- blurred or double vision; loss of side (peripheral) vision
- drooping eyelid (ptosis) caused by pressure on nerves leading to the eye
- numb feeling on the face
- dementia
- drowsiness
- enlarged head

- eating excessive (hyperphagia) or abnormally small (hypophagia) amounts of food
- seizures

The specific symptoms associated with hormone-secreting tumors will vary depending on which hormones are being over-produced. Symptoms related to hormonal imbalance include:

- excessive sweating
- loss of appetite
- loss of interest in sex
- inability to tolerate cold temperatures
- nausea
- menstrual problems
- excessive thirst
- frequent urination
- dry skin
- constipation
- premature or delayed puberty
- delayed growth in children
- milk secretion in the absence of pregnancy or breast feeding (galactorrhea)
- reduced strength
- mood alterations (**depression**, anxiety, unstable emotions)
- muscle pain
- low blood sugar (sudden occurrence of shakiness and sweating)

Patients who have sudden pituitary failure caused by bleeding or tissue death (pituitary apoplexy also known as Sheehan's syndrome) may experience very severe headaches, confusion, loss of sight, and drowsiness. This condition is considered an emergency.

Tumors that secrete growth hormone cause a condition called acromegaly. This long-term condition is characterized by enlargement of the nose, ears, jaws, toes, and fingers. Joint pain, blood sugar imbalances, high blood pressure, carpal tunnel syndrome, and airway blockages can result.

Diagnosis

As many as 40% of all pituitary tumors do not release excessive quantities of hormones into the blood. Known as clinically nonfunctioning, these tumors are difficult to distinguish from tumors that produce similar symptoms. They may grow to be quite large before they are diagnosed.

The diagnosis of pituitary tumors is based on:

- the patient's own observations and medical history
- physical examination
- laboratory studies of the patient's blood and brain/spinal fluid (cerebrospinal fluid)
- x rays of the skull and other studies that provide images of the inside of the brain (CT, MRI)
- vision tests
- urinalysis

Treatment team

The treatment team for pituitary tumors may include a neuroendocrinologist, endocrinologist, neurosurgeon, oncologist, radiation oncologist, nurse oncologist, psychiatrist, psychological counselor, and social worker.

Clinical staging, treatments, and prognosis

Clinical staging

Because most pituitary tumors are benign, there is no clinical staging system.

Treatments

Treatment is determined by the type of tumor, the type of hormone being released, and whether or not the tumor has invaded tissues next to the pituitary gland. The goals of treatment are to normalize hormone levels and reduce the size of (or remove) the tumor. Treatment options include surgery, radiation, and/or medication. Some pituitary tumors stabilize without treatment. Small tumors that are not causing significant symptoms may be watched only.

Surgery is usually used to remove all or part of a tumor within the gland or the area surrounding it. Surgery may be combined with **radiation therapy** to treat tumors that extend beyond the pituitary gland. A neurosurgeon will operate immediately to remove the tumor or pituitary gland (hypophysectomy) of a patient whose vision is deteriorating rapidly. Approximately 96% of the surgeries are performed through the nose (transsphenoidal). If the tumor is large, the skull may be opened (**craniotomy**) for tumor removal. Removal or destruction of the pituitary gland requires life-long hormone replacement therapy. The most common complications of surgery are leakage of cerebrospinal fluid through the nose and inflammation of the membranes that surround the brain and spinal column (meningitis).

Radiation therapy is not as effective as surgery and is usually reserved for tumors that have not responded to other treatments and those that recur. Radioactive pellets

KEY TERMS

Adenoma—A tumor that is derived from glandular tissue.

Agonist—A drug that increases the effectiveness of another drug or chemical.

Benign—A term used to describe a noncancerous growth.

Carney complex—A genetic disorder characterized by myxomas, spotty pigmentation of the skin and mucous membranes, and endocrine overactivity.

Dopamine—A neurotransmitter that is a chemical messenger in the brain.

Hormone—A chemical that is produced and released by one organ to regulate the function of another organ.

Invasive—A descriptive term for tumors that spread to nearby structures.

McCune-Albright syndrome—A genetic disorder that includes bone, endocrine, and skin abnormalities. Some individuals with this syndrome show the effects of excessive secretion of pituitary growth hormone.

Multiple endocrine neoplasia syndrome type I—An inherited disorder that affects the endocrine glands. The pituitary gland becomes overactive in about one-sixth of the individuals with this syndrome.

Nelson's syndrome—An endocrine disorder characterized by increase secretion of ACTH and melanocyte stimulating hormone by the pituitary gland.

can be implanted in the brain to treat the tumor. Selected patients are treated with proton beam radiosurgery that uses high energy particles in the form of a high energy beam to destroy an overactive pituitary gland. **Fatigue**, upset stomach, **diarrhea**, and nausea are common complaints of patients having radiation therapy. Radiation therapy to the brain can damage certain brain tissues.

Dopamine agonists, drugs that increase the effect of the brain chemical dopamine, are effective in treating tumors that release hormones. These drugs can reduce symptoms caused by a pituitary tumor and reduce the size of the tumor. Commonly used dopamine agonists include bromocriptine, pergolide, and cabergoline. Cabergoline is the most effective and produces fewer side effects than the other two drugs. Side effects associated with dopamine agonists include nausea, vomiting, and light-headedness when rising (postural hypotension). Acromegaly may be treated with somatostatin and other drugs derived from somatostatin (analogues). Tumors, and the symptoms they are causing, return when drug use is stopped. Patients should wear medical identification tags identifying their condition and the hormonal replacement medicines they take.

The common treatments for specific pituitary tumors are:

- Prolactin-secreting adenoma. Prolactinomas are treated with a dopamine agonist. Surgical treatment is used if the drug fails or causes intolerable side effects.
- Gonadotropin-secreting adenoma. Small tumors are not treated unless they are causing symptoms. Large tumors and small tumors that are causing symptoms are treated surgically. Radiation therapy may be used.
- Adrenocorticotropic hormone-secreting adenoma. Surgery is the treatment of choice. Medications that prevent adrenal hormone production or radiation therapy may be used if surgery fails.
- Growth hormone-secreting adenoma. Surgery is the treatment of choice. Medications (dopamine agonists, somatostatins) or radiation therapy may be used.
- Thyroid stimulating hormone-secreting adenoma. Surgery, with or without radiation therapy, is the treatment of choice. Although somatostatin treatment may reduce hormone levels, it fails to shrink the tumor.
- Nonsecreting adenoma. Surgery is the treatment of choice. In general, medications are not effective for this type of tumor. Radiation therapy may be used to prevent tumor recurrence.
- Pituitary carcinoma. Carcinoma is treated with standard cancer radiation therapy and chemotherapy.
- Craniopharyngiomas. These tumors are difficult to treat. Due to the nature of craniopharyngiomas, surgery is often incomplete and needs to be complemented by radiation therapy.

Prognosis

Pituitary tumors are usually curable. Pituitary adenomas that secrete adrenocorticotropic hormone are frequently persistent and have a high rate of recurrence. Approximately 5% of pituitary adenomas invade nearby tissues and grow to large sizes, making them more difficult to treat and subject to frequent recurrences. Metastasis of most pituitary tumors is very rare. However, pituitary carcinomas can metastasize and are associated with a poor prognosis.

Alternative and complementary therapies

Alternative and complementary therapies have not been shown to be effective in treating pituitary tumors.

QUESTIONS TO ASK THE DOCTOR

- Is my tumor cancerous? Is it invasive?
- What are my treatment options?
- What are the risks and side effects of these treatments?
- Is surgery really necessary?
- Which surgical approach will you use?
- How experienced are you at performing pituitary surgery?
- How will I feel immediately following surgery?
- Will I need to take medication for the rest of my life?
- How long will it take for my symptoms to go away?
- Will I be able to have children?
- Is it safe to become pregnant while taking this medication?
- How will pregnancy affect my tumor?
- What medications can I take to relieve treatment side effects?
- Are there any clinical studies underway that would be appropriate for me?
- What is the chance that the tumor will recur?
- How will recurrence be detected?
- How often will I have follow-up examinations?

For more comprehensive information, the patient should consult the book on complementary and alternative medicine published by the American Cancer Society listed in the Resources section.

Coping with cancer treatment

The patient should consult his or her treatment team regarding any side effects or complications of treatment. Patients may want to consult a psychotherapist and/or join a support group to deal with the emotional consequences of cancer and its treatment.

Clinical trials

There are two active **clinical trials** studying pituitary tumors are studying the safety and effectiveness of antineoplastons. Study #BRI-BT-9 is open to patients with serious or life-threatening brain tumors. Study #BRI-NE-2 is open to patients who have metastatic or incurable **neuroendocrine tumors**. The National Cancer Institute web site has information on these and other studies. Patients should consult with their treatment teams to determine if they are candidates for these or any other ongoing studies.

Special concerns

Long-term low levels of sex hormones (hypogonadism) can have negative effects on bone density and the cardiovascular system. The effect a pituitary tumor has on fertility is a concern for both men and women. Women taking medications to treat pituitary tumors need to question their physicians regarding the potential effect the medications may have on an unborn baby.

See also Mutliple endocrine neoplasia syndromes.

Resources

BOOKS

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DeAngelis, Lisa, and Jerome Posner. "Cancer of the Central Nervous System and Pituitary Gland." In *Clinical Oncology*, edited by Raymond Lenhard, Robert Osteen, and Ted Gansler. Atlanta: American Cancer Society, 2004, pp.653–703.

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Molitch, Mark, editor. *Endocrinology and Metabolism Clinics of North America: Advances in Pituitary Tumor Therapy*. Philadelphia: W.B. Saunders Company, 1999.

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Wardlaw, Fred, P. Wardlaw, and S. Wardlaw. "Diagnosis and Treatment of Pituitary Tumors." *The Journal of Clinical Endocrinology & Metabolism* 84 (November 1999): 3859-66.

ORGANIZATIONS

American Brain Tumor Association. 2770 River Road, Des Plaines, IL 60018. (800) 886-2289. <http://www.abta.org>.

American Cancer Society. 1599 Clifton Road NE, Atlanta, GA 30329. (800) ACS-2345. <http://www.cancer.org>.

Brain Tumor Information Services. Box 405, Room J341, University of Chicago Hospitals, 5841 S. Maryland Avenue, Chicago, IL 60637. (312) 684-1400.

Cancer Research Institute, National Headquarters. 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

National Institutes of Health. National Cancer Institute. 9000 Rockville Pike, Bethesda, MD 20982. Cancer Information Service: (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

Maureen Haggerty
Belinda Rowland, Ph.D.

Plasma cell dyscrasias, or plasma cell neoplasms *see* **Multiple myeloma; Waldenstrom's macroglobulinemia**

Plasmacytoma *see* **Multiple myeloma**

Plasmapheresis *see* **Pheresis**

Pleural biopsy

Definition

The pleura is the membrane that lines the lungs and chest cavity. A pleural **biopsy** is the removal of pleural tissue for examination and eventual diagnosis.

Purpose

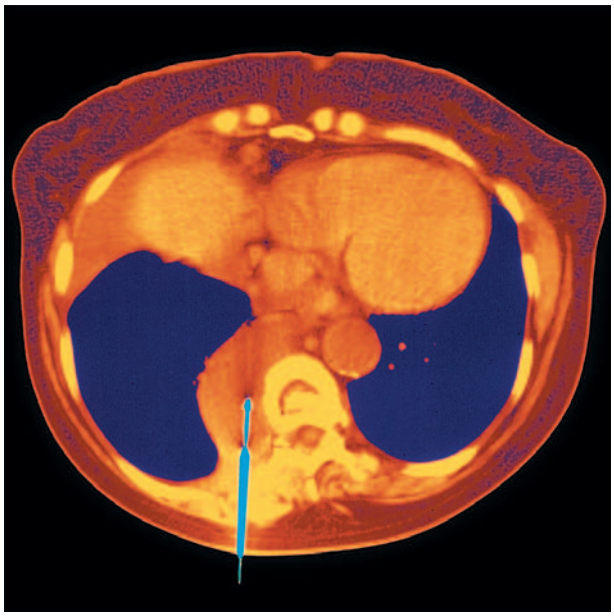
Pleural biopsy is performed to differentiate between benign (noncancerous) and malignant (cancerous) disease, to diagnose viral, fungal, or parasitic diseases, and to identify a condition called collagen vascular disease of the pleura. It is also ordered when a chest **x ray** indicates a pleural-based tumor, reaction, or thickening of the pleura.

Precautions

Because pleural biopsy—especially open pleural biopsy—is an invasive procedure, it is not recommended for patients with severe bleeding disorders.

Description

Pleural biopsy is usually ordered when pleural fluid obtained by another procedure called **thoracentesis** (aspiration of pleural fluid) suggests infection, signs of cancer, or tuberculosis. However, the procedure is most successful in diagnosing pleural tuberculosis (with a sensitivity up to 75%) rather than pleural malignancy (40–50% sensitivity).



Colored computed tomography (CT) scan of an axial section through the chest, showing a lung biopsy being taken by bronchoscope. The front of the chest is at the top, and the heart is at the lower center (appearing orange). The bronchoscope (blue) has penetrated the back of the patient and has entered a tumor (orange). At the tip of the bronchoscope is a biopsy needle. *(Copyright Mehau Kulyk, Science Source/Photo Researchers, Inc. Photo reproduced by permission.)*

The procedure most often performed for pleural biopsy is called a percutaneous (passage through the skin by needle puncture) needle biopsy or closed needle biopsy. This procedure can only sample the outer pleural membrane (parietal pleura), and the size of the tissue sample obtained is relatively small.

Although the biopsy needle itself remains in the pleura for less than one minute, the procedure takes 30–45 minutes. This type of biopsy is usually performed by a physician at bedside if the patient is hospitalized or in an outpatient setting under local anesthesia.

The actual procedure begins with the patient in a sitting position, shoulders and arms elevated and supported. The skin overlying the biopsy site is anesthetized and a small incision is made to allow insertion of the biopsy needle. This needle is inserted with a cannula (a plastic or metal tube) until fluid is removed. Then the inner needle is removed and a trocar (an instrument for withdrawing fluid from a cavity) is inserted to obtain the actual biopsy specimen. As many as three separate specimens are taken from different sites during the procedure. These specimens are then placed into a fixative solution and sent to the laboratory for tissue (histologic) examination.

Although used less frequently than the closed needle biopsy, an open pleural biopsy may be performed surgi-

KEY TERMS

Aspiration—Drawing out of fluid from a cavity by suction.

Endotracheal—Placed within the trachea, also known as the windpipe.

Pulmonary—Pertaining to the lungs.

QUESTIONS TO ASK THE DOCTOR

- What is the purpose of this test?
- Is the test dangerous?
- How do I prepare for the test?
- How long will the test take?
- How soon will I get my test results?

cally, in the operating room, when a larger tissue sample is required. The incision is larger than that required for a closed needle biopsy, and an endotracheal tube is inserted through the windpipe to assure proper breathing during the procedure. The procedure takes two to three hours, is more invasive, and requires general anesthesia and hospitalization for one or more days. Open biopsy is sometimes performed when there is no **pleural effusion** (an accumulation of fluid between the pleural layers) or when a direct view of the pleura and lungs is required.

Another procedure, called **thoracoscopy**, involves pleural biopsy under direct visualization through a thoracoscope. This procedure is highly accurate (sensitivity as high as 91%) in diagnosing both benign and malignant pleural disease. As in open needle biopsy, however, it requires general anesthesia and is usually used only after other diagnostic procedures fail.

Preparation

Preparations for this procedure vary, depending on the type of procedure requested. Closed needle biopsy requires little or no preparation. Open pleural biopsy, which is performed in a hospital, requires fasting (no solids or liquids) for 8–12 hours before the procedure because the stomach must be empty before general anesthesia is administered.

Aftercare

Potential complications of this procedure include bleeding or injury to the lung, or a condition called pneumothorax, in which air enters the pleural cavity (the space between the two layers of pleura lining the lungs and the chest wall). Because of these possibilities, a chest x ray is always performed after the procedure (closed or open biopsy). Also, it is important for the patient is to report any shortness of breath and for the nurses to note any signs of bleeding, decreased blood pressure, or increased pulse rate during the recovery period.

Risks

Risks for this procedure include respiratory distress on the side of the biopsy, as well as bleeding, possible shoulder pain, infection, pneumothorax (immediate), or **pneumonia** (delayed). Risk increases with stress, obesity, smoking, chronic illness, and the use of some medications (such as insulin, tranquilizers, and antihypertensives).

Normal results

Normal findings indicate no evidence of any pathologic or disease conditions in the pleural cavity.

Abnormal results

Abnormal findings include tumors called neoplasms (any new or abnormal growth) that can be either benign or malignant. Pleural tumors are divided into two categories: primary (**mesothelioma**), or metastatic (spreading to the pleural cavity from a site elsewhere in the body). These tumors are often associated with pleural effusion, which itself may be caused by pneumonia, heart failure, cancer, or blood clot in the lungs (pulmonary embolism).

Other causes of abnormal findings include viral, fungal, or parasitic infections, and tuberculosis.

Resources

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Peek, Giles, Sameh Morcos, and Graham Cooper. "The Pleural Cavity." *British Medical Journal*. 320 (May 2000): 1318–1321.

ORGANIZATIONS

Alliance for Lung Cancer Advocacy, Support, and Education. P.O. Box 849, Vancouver, WA 98666. 800–298–2436. <http://www.alcase.org>.

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. 800–ACS–2345 <http://www.cancer.org>.

American College of Chest Physicians. 3300 Dundee Road, Northbrook, IL 60062–2348. 847–498–1400. <http://www.chestnet.org>.

American Lung Association. 1740 Broadway, New York, NY 10019–4374. 800–LUNG–USA (800–586–4872) <http://www.lungusa.org>.

Janis O. Flores

Pleural effusion

Description

Pleural effusion is the accumulation of fluid in the pleural space. The pleural space is the region between the outer surface of each lung (visceral pleurae) and the membrane that surrounds each lung (parietal pleurae). Under normal conditions, the pleurae are kept wet with pleural fluid to allow movement of the lungs within the chest. The pleural fluid comes from cells that make up the pleurae. Pleural fluid is continuously being produced and removed, a process that is precisely controlled by many factors. Cancer can interfere with this delicate balance within the pleural space causing fluid to accumulate.

Cancer is responsible for 40% of all pleural effusions, which are then called malignant pleural effusions. Pleural effusion is the first symptom of cancer for up to 50% of the patients. Thirty-five percent of the cases of malignant pleural effusion are caused by lung cancer, 23% by **breast cancer**, and 10% by **lymphoma**.

Chest x rays and computed tomography scans may be performed to diagnose pleural effusion. **Thoracentesis**, the removal of pleural fluid through a long needle, is usually performed for diagnostic purposes. Fluid removed by thoracentesis will be sent to the lab to be thoroughly evaluated. **Thoracoscopy**, in which a wand-like lighted camera (endoscope) is inserted through the chest, may be conducted to diagnose pleural effusion. During thoracoscopy, samples (**biopsy**) of pleura may be taken.

Pleural effusion can hinder the normal function of the lungs. Symptoms of pleural effusion include chest pain, chest heaviness, breathing difficulties, and a dry cough. Patients with malignant pleural effusions tend to be weak and have a short-span life expectancy. The prognosis depends on the type of cancer. Sixty-five percent of patients with malignant pleural effusions die within three months and 80% die within six months. However, patients with pleural effusion related to breast cancer have a longer life expectancy.

Causes

Malignant pleural effusions are most often associated with lymphomas, leukemia, breast cancer, gastrointestinal cancer, lung cancer, and **ovarian cancer**. For the majority of patients, pleural effusion occurs in the lung on the same side as the cancer. For one third of the patients, pleural effusion occurs in both lungs.

Pleural effusion in cancer patients can be caused by several different conditions. Blockage of the lymphatic system, a series of channels for drainage of body fluids, interferes with the removal of pleural fluid. Blockage of the veins of the lungs increases the pressure at the pleurae which causes fluid accumulation. Cancerous cells may seed onto pleurae and cause inflammation which increases fluid in the pleural space. High numbers of cancerous cells may collect in the pleural space (tumor cell suspensions) which causes extra fluid to be released. Accumulation of fluid in the abdominal cavity may cross over to the pleural space.

Treatments

Management of pleural effusion strives to relieve symptoms and improve quality of life. Cure is not always possible. The treatment method depends on the patient's age, prognosis, and location of the first tumor. Treatment for patients with pleural effusion who are asymptomatic (do not have symptoms) consists solely of observation.

Treatment options for pleural effusion include:

- Thoracentesis. Removal of the excess pleural fluid often relieves the symptoms of pleural effusion. However, effusion usually recurs within a few days. Repeat thoracentesis is not recommended, unless the patient has end-stage disease.
- Tube thoracostomy. A tube is inserted through the chest and into the pleural space to drain pleural fluid. When used alone, recurrence is very common.
- Indwelling pleural catheters. A thin flexible tube (catheter) is placed between the pleural cavity and the chest skin to allow drainage of pleural fluid. This method allows for continual drainage of pleural fluid without much pain.
- **Pleurodesis**. After tube thoracostomy, one of any number of chemicals (sclerosing agents) is put into the

KEY TERMS

Parietal pleurae—The membrane that surrounds each lung.

Pleural space—The space between the visceral and parietal pleurae.

Visceral pleurae—The outer surface of each lung.

pleural space to cause the visceral and parietal pleurae to stick together. Chemical pleurodesis is considered to be the treatment of choice for patients with malignant pleural effusion.

- Pleurectomy. Surgical removal of the parietal pleura through an incision in the chest wall (**thoracotomy**) is nearly 100% effective. Pleurectomy is not routinely performed and is reserved for patients for whom other treatments have failed. To be eligible for pleurectomy, the patient must have a long life expectancy and be able to tolerate major surgery.
- Pleuroperitoneal shunt. This procedure places a rubber tube between the pleural space and the abdominal cavity. A pump is used to move excess fluid out of the pleural space and into the abdominal cavity, where it would be absorbed. The patient must press the pump for several minutes four times daily. Although not frequently used, this is an effective treatment for cases that failed tube thoracostomy and pleurodesis.
- External radiation. Patients who have pleural effusion caused by blockage of a lymph duct may be treated by **radiation therapy**. External radiation therapy is successful for patients with pleural effusion related to lymphoma.
- Supportive care. Patients with end-stage cancer may not receive treatment for pleural effusion. Pain medications and oxygen therapy can be provided to keep the patient comfortable.

Belinda Rowland, Ph.D.

Pleural fluid analysis *see* **Thoracentesis**

Pleurodesis

Definition

Pleurodesis is the adherence of the outer surface of a lung to the membrane surrounding that lung, which is performed to treat the buildup of fluid around the lung.

Purpose

The pleural space is the region between the outer surface of each lung (visceral pleurae) and the membrane that surrounds each lung (parietal pleurae). Under normal conditions, the pleurae are kept wet with pleural fluid to allow movement of the lungs within the chest. **Pleural effusion**, the accumulation of fluid in the pleural space, is most commonly caused by cancer. Pleurodesis causes the pleurae to stick together, thereby eliminating the pleural space and preventing fluid accumulation. Chemical pleurodesis is considered to be the standard of care for patients with malignant pleural effusion.

Description

Before pleurodesis is conducted, all pleural fluid must be removed. This is achieved by inserting a chest tube through the skin and into the pleural space (thoracostomy). Insertion of the chest tube is carried out in the hospital. The patient is awake during the procedure. The skin is sterilized and a local pain killer is injected into the skin and underlying tissue. A small cut is made into the skin and a tube is placed into the pleural space. Fluid is withdrawn and the tube remains in place until all pleural fluid is drained, which usually takes two to five days. After the chest tube is inserted, the patient may either remain in the hospital or be allowed to return home with instructions on how to care for the tube. A chest **x ray** may be taken to ensure that all the fluid has been drained.

Pleurodesis is achieved by putting one of any number of chemicals (sclerosing agents or sclerosants) into the pleural space. The sclerosant irritates the pleurae which results in inflammation (pleuritis) and causes the pleurae to stick together. The patient is given a narcotic pain reliever and lidocaine, a local pain killer, is added to the sclerosant. A variety of different chemicals are used as sclerosing agents. There is no one sclerosant that is more effective or safer than the others. Commonly used sclerosants and their success rates are:

- Talc: 90% to 96%
- Nitrogen mustard: 52%
- Doxycycline: 90%
- **Bleomycin**: 84%
- Quinacrine: 70% to 90%

After the sclerosant has been put through the chest tube, the tube is closed. The patient may be asked to change position every 15 minutes for a two-hour time period. This was believed to be necessary to achieve an even distribution of sclerosant in the pleural space. However, recent evidence suggests that the sclerosant spreads

KEY TERMS

Pleural effusion—The abnormal buildup of fluid within the pleural space.

Pleural space—The space between the outer surface of each lung and the membrane that surrounds each lung.

Sclerosant—A chemical that causes the membranes of the pleural space to stick together.

throughout the pleural space immediately. Afterward, the chest tube is reopened and the sclerosant is sucked out of the pleural space. The tube remains in place for several days to allow all fluid to drain. Once drainage slows down, the chest tube is removed and the wound edges stitched (sutured) back together.

Aftercare

The patient should keep the wound from the chest tube clean and dry until it heals. Also, the patient should watch for signs of wound infection such as redness, swelling, and/or drainage, and be alert to symptoms indicating that the effusion recurred.

Risks

Complications of pleurodesis are uncommon and include infection, bleeding, acute respiratory distress syndrome, collapsed lung (pneumothorax), and respiratory failure. In addition, other complications may be specific for each sclerosant. Talc and doxycycline can cause **fever** and pain. Quinacrine can cause low blood pressure, fever, and hallucination. Bleomycin can cause fever, pain, and nausea. Severe respiratory complications can be fatal.

Normal results

Tube thoracostomy with pleurodesis is the most effective method to treat malignant pleural effusion. Successful pleurodesis prevents the recurrence of pleural effusion which relieves symptoms thereby improving quality of life.

Abnormal results

If drainage of sclerosant from the chest tube exceeds approximately one cup, the pleurodesis was unsuccessful and needs to be repeated. Pleurodesis may fail because of:

QUESTIONS TO ASK THE DOCTOR

- Will I be hospitalized the entire time?
- How long will I be hospitalized?
- Is it possible to do this on an outpatient basis?
- How uncomfortable is the chest tube?
- Will I be given pain medication as needed?
- Will having a chest tube limit my movements in any way?
- Will I be confined to bed?
- Which sclerosant will you be using?
- Why are you using this sclerosant?
- What are the side effects of this sclerosant?
- What is the success rate associated with this sclerosant?
- How painful is the pleurodesis process?

- trapped lung, in which the lung is enclosed in scar or tumor tissue
- formation of isolated pockets (loculation) within the pleural space
- loss of lung flexibility (elasticity)
- production of large amounts of pleural fluid
- extensive spread (**metastasis**) of pleural cancer
- improper positioning of the tube
- blockage or kinking of the tube

Resources

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Belinda Rowland, Ph.D.

Plicamycin

Definition

Plicamycin is an antibiotic also known as mithramycin; it is sold under the trade name Mithracin. The medicine kills cancer cells. It may be used to treat cancer of the testicles. In addition, it may be used as treatment for **hypercalcemia**. Hypercalcemia is a condition characterized by high levels of calcium in the blood.

Purpose

Plicamycin is a drug used to treat **testicular cancer** in patients who are not good candidates for either surgery or x-ray therapy. It was first approved for this use by the Food and Drug Administration (FDA) in May 1970.

Plicamycin is also used to treat hypercalcemia. Many patients with hypercalcemia also have elevated levels of calcium in the urine. As treatment for this condition, plicamycin may not be a doctor's first choice. The reason for this is that plicamycin may cause serious side effects. Newer medicines, known as **bisphosphonates**, can effectively resolve hypercalcemia and these have fewer side effects. However, some patients cannot tolerate bisphosphonates. These patients may be given plicamycin.

Description

Plicamycin is produced by a bacterium known as *Streptomyces argillaceus*. It interacts chemically with the DNA in cells and so interferes with the production of RNA. It is thought that plicamycin also works by making tumor cells more sensitive to tumor necrosis factor (TNF), a nonantibody protein secreted by cells in the immune system that kills tumor cells. Plicamycin lowers levels of calcium in the blood by affecting the formation of new bone cells and interfering with the activities of certain hormones.

A new form of plicamycin, mithramycin SK, was developed at the University of Kentucky in 2003 from a genetically modified form of *S. argillaceus*. Mithramycin SK is a more effective antitumor drug than the original plicamycin.

Recommended dosage

For testicular cancer, some doctors give 25 micrograms per kilograms of body weight every two to four days to start. However, if the patient has kidney or liver problems, these doctors may give 12.5 micrograms per kilogram instead. Others administer 25 to 30 micrograms per kilograms of body weight every eight to ten days. Others may give as much as 50 micrograms per kilogram of body weight per dose for approximately eight doses every other day.

For high levels of calcium in the blood and urine, fifteen to twenty-five micrograms per kilogram of body weight may be given every day for three or four days. Following this, additional medication may be required approximately once a week.

Precautions

This medication is often not given to patients with problems with blood clotting or with the bone marrow. Plicamycin should not be given to pregnant women, nursing mothers, or children younger than fifteen years of age. The medicine should be used with caution in patients with liver or kidney problems. To lessen side effects to the digestive tract, the medicine may be administered over the course of four to six hours. Additional precautions should be followed to minimize the chances that the medicine will cause blistering.

Since people taking plicamycin are at increased risk of developing an infection and of having bleeding problems, they should avoid people who do have an infection. In addition, they should wash their hands before touching the inside of their mouth, their eyes, or their nose. Also, they should not take aspirin or over-the-counter preparations containing aspirin. In addition, they should attempt not to cause bleeding, for example when they brush and floss their teeth or when they shave.

Doctors should carefully monitor blood counts, liver function, and kidney function for patients given more than one dose of plicamycin.

Certain precautions should be followed by all patients. For example, plicamycin probably should not be taken by anyone who is living is a household with someone who has recently received oral polio vaccine, as there is a risk of transmission of the polio virus. The

KEY TERM

Hypercalcemia—A condition characterized by high levels of calcium in the blood.

person receiving plicamycin should wear a face mask if she or he is going to be in close proximity to anyone who has recently received the oral polio vaccine for an extended period. In addition, vaccines containing live organisms should not be given to anyone who is taking plicamycin or anyone who recently took plicamycin.

Side effects

The side effects of plicamycin include a tendency for abnormal bleeding. There may be low levels of calcium, potassium, and phosphorous in the blood, as well as other blood problems. The face may become flushed. Kidney or liver problems may develop. If bleeding does occur there may be damage to the surrounding skin.

Other side effects may include **diarrhea**, loss of appetite (anorexia), nausea and vomiting, and soreness of the mouth. Muscle cramps and abdominal cramps may develop, although these are likely to disappear as the body gets used to the medication. Uncommon side effects include pain, soreness at the injection side, **fever**, weakness, headache, depressed mood, **fatigue**, and drowsiness.

The side effects of this medicine tend to increase as the dose of the medicine exceeds 30 micrograms per kilogram.

It is important to notify the doctor if any of the following symptoms of plicamycin overdose appear: vomiting of blood; yellow eyes or skin; bloody, or black, tarry stools; swelling of the face or redness of the face; skin rash; or the appearance of tiny red spots on the skin.

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ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657-3000. <www.ashp.org>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

Bob Kirsch
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Ploidy analysis

Definition

Ploidy analysis is a test that measures the amount of DNA in tumor cells. It is also called DNA ploidy analysis.

Purpose

DNA ploidy analysis is used in addition to the traditional grading system as another way to evaluate how malignant a tumor might be. The advantage of this test is that it provides a numeric, and therefore objective, evaluation of how aggressive the cancer might be. Because this test was relatively new in 2001, and the significance of information gained by this test was not completely understood, this test had not yet replaced traditional systems of **tumor grading**. It would be used only to supplement those tests in order to give the doctor as much information about the nature of the tumor as possible. Doctors may also use this test to help predict how a tumor may respond to the planned therapy.

Precautions

This test requires a certain sample size in order to be performed; the specimens acquired in some biopsies may

KEY TERMS

Aneuploid—Any number of chromosomes except the normal two sets.

Diploid—Two sets of 23 chromosomes. The normal amount in a human cell.

Ploidy—The number of sets of 23 chromosomes a human cell has.

Tetraploid—Four sets of chromosomes. The normal amount in a human cell that is about to divide to form two new cells.

QUESTIONS TO ASK THE DOCTOR

- Why did you order this test? What are you hoping it will tell us?
- What do the results mean?
- How much faith should I put in these results?
- Am I taking any medications that could influence the results of this test?
- Will my insurance company pay for this test?

not provide enough material to run the test. It is also important in this test that only tumor material is used to create the population of cells which are analyzed, as any healthy tissue included can significantly affect the results. Interpretation of the numeric results of this test is still somewhat controversial. There is no commonly accepted system for interpreting the results; in addition, the results of the test can vary greatly from one part of a tumor to another.

The way the test should be used for optimum results in the management of cancer patients remained questionable due to many unexplored issues, and results due to the lack of data accumulated so early into its history. Although research has shown that in general, patients whose tumors have lots of cells with abnormal amounts of DNA have shorter survival times, the results of the test have not, for the most part, been that successful in predicting how an individual patient will do.

Description

Ploidy analysis is performed on a sample of the tumor to determine how many of the cells have the normal amount of DNA and how many have more or less than the normal amount (called aneuploid). Cancerous cells are rapidly dividing cells. When cells divide there is a period before the actual division during which the cells have twice the normal amount of DNA. Tumors with higher proportions of aneuploid cells are generally considered to be more aggressive tumors.

Taking a sample of a tumor is called a **biopsy**. How and where that is done depends on where the tumor is located. Tissue from the surface of body cavities like the mouth or the vagina can be easily sampled from a simple scraping, in a doctor's office. For some types of tumors (such as in **breast cancer**) it is possible to extract enough cells with a needle and syringe. Often, however, a surgical biopsy will need to be performed in the hospital. The tissue removed will be taken to a laboratory and analyzed.

Preparation

Patient preparation for the collection of a tumor sample through biopsy will vary depending on the site of the tumor. Most biopsies call for little that the patient will need to do. For biopsies of internal organs the patient may need to avoid eating after midnight before the test, in case a complication occurs and surgery may be necessary. Patients should try not be fearful of the collection of the sample. Doctors will make the procedure as painless as possible by using appropriate anesthetic.

Aftercare

There can be a little soreness at the biopsy site for a few days following the procedure; acetominophen or another over-the-counter painkiller can be used if the patient feels a need for pain relief. If the site becomes swollen, red, or hot to the touch it may be infected and the patient should contact a physician.

Risks

The risks involved in this test are only the risks inherent in having a biopsy. Since this procedure uses tissue obtained through a biopsy already being performed for the purpose of grading the tumor, there are no additional risks to the patients involved as a result of the test. This test can also be performed on stored biopsy tissues that were obtained at some previous time.

Normal results

Normal cells, most of the time, have two sets of 23 chromosomes, one from each parent, for a total of 46 chromosomes. Normal cells contain four sets–or 92 total chromosomes–for a very brief time right before they divide. Normal tissues have a largely homogenous population of cells containing 46 chromosomes, with a very small percentage of dividing cells that contain 92.

Abnormal results

Tumors have lots of cells that are in the process of reproducing, so tumor tissues typically have a significant population of cells, containing 4 sets of chromosomes, that are about to divide, in addition to the large population of normal cells containing 2 sets of chromosomes. Tumor cells can also contain numerous other variations of normal. Any tissue comprised of significant numbers of cells that have anything but two sets of chromosomes would be considered abnormal.

See also DNA flow cytometry.

Resources

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Pneumonectomy

Definition

Pneumonectomy is the surgical removal of a lung.

Purpose

Pneumonectomy is most often used to treat lung cancer when less radical surgery cannot achieve satisfactory results. It also may be the most appropriate treatment for a tumor that is located near the center of the lung and that affects the pulmonary artery or veins, which transport blood between the heart and lungs. For the treatment of cancer, pneumonectomy may be combined with **chemotherapy** or **radiation therapy**. Pneumonectomy may also be the treatment of choice when traumatic chest injury has damaged the main air passage (bronchus) or the lung's major blood vessels so severely that they cannot be repaired. A form of this procedure known as extrapleural pneumonectomy is often used to treat malignant **mesothelioma**.

Precautions

Before scheduling a pneumonectomy, the surgeon reviews the patient's medical and surgical history and orders a number of tests to determine how successful the surgery is likely to be.

Blood tests, a bone scan, and **computed tomography** (CT) scans of the head and abdomen reveal whether the cancer has spread beyond the lungs. Positron emission tomography scanning (PET) is also used to help "stage" the disease. Cardiac screening indicates how well the patient's heart will tolerate the procedure, and extensive pulmonary testing (breathing tests and quantitative ventilation/perfusion scans) predicts whether the remaining lung will be able to compensate for the body's diminished breathing capacity.

Because extrapleural pneumonectomy is such an invasive operation, the patient must have no serious illness other than the cancer the surgery is designed to treat.

Description

Traditional pneumonectomy removes only the diseased lung. A more complex surgery generally performed in specialized medical centers, extrapleural pneumonectomy also removes:

- a section of the membrane (pericardium) covering the heart
- a portion of the muscular partition (diaphragm) that separates the chest and abdomen
- the membrane (parietal pleura) that lines the affected side of the chest cavity

General anesthesia is given to a patient undergoing either of these procedures. An intravenous (IV) line inserted into one arm supplies fluids and medication throughout the operation, which usually lasts between one and three hours; extrapleural pneumonectomies may last up to six hours.

The surgeon begins the operation by cutting a large opening on the side of the chest where the diseased lung is located. This posterolateral **thoracotomy** incision extends from below the shoulder blade, around the side of the patient's body, and along the curvature of the ribs at the front of the chest. Sometimes removing part of the fifth rib gives the surgeon a clearer view of the lung and makes it easier to remove the diseased organ.

A surgeon performing a traditional pneumonectomy then:

- deflates (collapses) the diseased lung
- ties off the lung's major blood vessels to prevent bleeding into the chest cavity
- clamps the main bronchus to prevent fluid from entering the air passage

KEY TERMS

Bronchopleural fistula—An abnormal connection between an air passage and the membrane that covers the lungs.

Empyema—Accumulation of pus in the lung cavity, usually as a result of infection.

Pleural space—A small space between the two layers of the membrane that covers the lungs and lines the inner surface of the chest.

Pulmonary embolism—Blockage of a pulmonary artery by a blood clot or foreign matter.

QUESTIONS TO ASK THE DOCTOR

- Why is it necessary to remove the whole lung?
- Why might I also need chemotherapy or radiation therapy?
- What should I do to prepare for this operation?
- How long will I have to stay in the hospital?
- Why is recovery such a slow process?

- cuts through the bronchus
- removes the lung
- staples or sutures the end of the bronchus that has been cut
- makes sure that air is not escaping from the bronchus
- inserts a temporary drainage tube between the layers of the pleura (pleural space) to draw air, fluid, and blood from the surgical cavity
- closes the chest incision

Besides removing the diseased lung, a surgeon performing an extrapleural pneumonectomy:

- cuts the pleura away from the chest wall
- removes parts of the pericardium and diaphragm on the affected side of the chest
- substitutes sterile synthetic patches for the tissue that has been removed
- closes the incision

Preparation

A patient who smokes must stop as soon as the disease is diagnosed.

A patient who takes aspirin or any other other blood-thinning medication must stop taking the medication about a week before the scheduled surgery, and patients may not eat or drink anything after midnight on the day of the operation.

Aftercare

Chest tubes drain fluid from the incision and a respirator helps the patient breathe for at least 24 hours after the operation. The patient may be fed and medicated intravenously. If no complications arise, the patient is transferred from the surgical intensive care unit (ICU) to a regular hospital room within one to two days.

A traditional pneumonectomy patient will probably be discharged within 10 days. A patient who has had an extrapleural pneumonectomy is likely to remain in the hospital between 10 and 12 days after the operation. While the patient is hospitalized, care focuses on:

- relieving pain
- monitoring to ensure that concentrations of oxygen in the blood do not become dangerously low (hypoexemia)
- encouraging the patient to walk in order to prevent formation of blood clots
- encouraging the patient to cough productively in order to clear accumulated lung secretions. If the patient cannot cough productively, the doctor uses a flexible tube (bronchoscope) to remove lung secretions and fluids (**bronchoscopy**).

Recovery is usually a slow process, with the remaining lung gradually taking on the tasks of the lung that has been removed and the patient gradually resuming normal, non-strenuous activities. Within eight weeks, a pneumonectomy patient who does not experience postoperative problems may be well enough to return to a job that is not physically demanding, but 60% of all pneumonectomy patients continue to experience marked shortness of breath six months after having surgery.

Risks

In the United States, the immediate survival rate from the surgery for patients who have had the left lung removed is between 96% and 98%. Due to the greater risk of complications involving the stump of the cut bronchus in the right lung, between 88% and 90% of patients survive removal of this organ.

Between 40% and 60% of pneumonectomy patients experience such short-term postoperative difficulties as:

- prolonged need for a mechanical respirator
- abnormal heart rate (cardiac arrhythmia), heart attack (myocardial infarction), or other heart problems
- pneumonia
- infection at the site of the incision
- a blood clot in the remaining lung (pulmonary embolism)
- an abnormal connection between the stump of the cut bronchus and the pleural space due to a leak in the bronchus stump (bronchopleural fistula)
- accumulation of pus in the pleural space (empyema)
- kidney or other organ failure

Over time, the chest's remaining organs may move toward the space created by the surgery. This condition is called postpneumonectomy syndrome, and a surgeon can correct it by inserting a fluid-filled prosthesis into the space the diseased lung occupied.

Normal results

The doctor will probably advise the patient to refrain from strenuous activities for a few weeks after the operation. Ribs that were cut during surgery will remain sore for some time.

A patient whose lungs have been weakened by noncancerous diseases like emphysema or chronic bronchitis may experience long-term shortness of breath as a result of this surgery.

Abnormal results

A patient who experiences a **fever**, chest pain, persistent cough, or shortness of breath, or whose incision bleeds or becomes inflamed, should notify his or her doctor immediately.

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Maureen Haggerty

Pneumonia

Description

One of the most common pulmonary complications affecting cancer patients, pneumonia is a potentially life-threatening inflammation of one or both lungs.

Causes

Serious side effects in cancer patients most often occur in the lungs and may indicate that the cancer is progressing or that the patient has developed a new problem. Both cancer and the therapies used to treat it can injure the lungs or weaken the immune system in ways that make cancer patients especially susceptible to the bacteria, fungi, viruses, and other organisms that cause pneumonia.

Tumors and infections can block the patient's airway or limit the lungs' ability to rid themselves of fluid and other accumulated secretions that make breathing difficult. Other factors that increase a cancer patient's risk of developing pneumonia include:

- radiation therapy
- chemotherapy
- surgery
- depressed white blood cell count (neutropenia)
- **antibiotics**
- steroids
- malnutrition
- limited mobility
- splenectomy-immune system deficits

The risk of developing pneumonia is greatest for a cancer patient who has one or more additional health problems.

Treatments

Pneumonia in cancer patients must be treated promptly in order to speed recovery and prevent complications that could arise if the inflammation were allowed to linger. Treatment always includes bed rest and coughing to expel phlegm and other fluids from the lungs (productive cough). To determine which course of treatment would be most appropriate, a doctor considers when symptoms first appeared, what pattern the illness has followed, and whether cancer or its treatments have diminished the patient's infection-fighting ability (**immune response**).

A doctor generally prescribes broad-spectrum oral antibiotics if:

- the patient has had a **fever** for less than a week
- pneumonia has not spread beyond the lung area where it originated
- the patient's cancer is responding to treatment
- the patient is otherwise in good health

The doctor uses a flexible tube (bronchoscope) to examine the lungs and airway (**bronchoscopy**) for inflammation, swelling, obstruction, and other abnormalities and washes the lungs (bronchoalveolar lavage) with a mucus-dissolving solution if:

- pneumonia is extensive, aggressive, or severe
- antibiotics don't clear the infection
- the patient is very ill

The doctor may also remove a small piece of lung tissue (transbronchial **biopsy**) for microscopic examination and cultures, and prescribe medication to combat fungal and viral organisms that might be responsible for the patient's symptoms. If the patient's condition continues to worsen, the doctor may remove additional lung tissue (thoracic needle biopsy or open lung biopsy) for microscopic analysis and cultures.

Alternative and complementary therapies

Non-medical treatments will not cure pneumonia but may relieve symptoms and make the patient more comfortable. All of these therapies require the treating doctor's approval.

ACCUPUNCTURE Accupuncture may relieve congestion and reduce **fatigue**.

ESSENTIAL OILS Added to a warm bath or vaporizer, essential oils of eucalyptus (*Eucalyptus globus*), lavender (*Lavandula officinalis*), or pine (*Abies sibirica*) can create a fragrant steam that helps the patient breathe more easily. Because steam inhalations can irritate the lungs, individuals who have asthma should not use them.

POSTURAL DRAINAGE A strenuous exercise that can help clear phlegm from the lungs, postural drainage should be practiced only with a doctor's approval and in the presence of a person who can provide support for a patient who becomes tired or weak.

Leaning over the side of the bed with forearms braced on the floor, the patient coughs up phlegm and spits it into a container. If the patient cannot cough productively enough to dislodge phlegm, the support person can help clear lung secretions by pounding gently on the patient's upper back. Postural drainage should be performed three times a day. Each session should last between five and 15 minutes, unless the patient tires or weakens sooner.

KEY TERMS

Antineoplastic—An agent that inhibits or prevents the maturation and proliferation of malignant cells.

Free radicals—Highly reactive molecules that act as agents of tissue damage.

Necrosis—The sum of all the morphological changes that indicate cell death.

Oncologist—A physician who specializes in the diagnosis and treatment of cancer patients.

Photodynamic therapy—Cancer treatment that uses the interaction between laser light and an agent that makes cells more sensitive to light.

Photosensitizing agents—Ultraviolet or sunlight-activated drugs used in the treatment of certain cancer types.

Porphyrins—Pigments found in the body that have an active affinity for metals.

Radiologically occult—Radiologically unapparent or undefined.

MASSAGE After the patient's fever has broken, gently massaging the upper back may relieve congestion and encourage productive cough.

HERBAL REMEDIES Homemade cough medicines (expectorants) containing licorice (*Glycyrrhiza glabra*), black cherry (*Prunus serotina*) bark, raw onions, honey, and other natural ingredients can relieve congestion and encourage productive cough. Because natural substances can be poisonous, they should be used only with a doctor's approval and according to label directions.

Eating raw garlic (*Allium sativum*) or taking garlic supplements is believed to strengthen the immune system. Echinacea, brewed as tea or taken in liquid or capsule form, may help some patients recover more quickly.

VITAMINS Zinc supplements and large doses of **Vitamins** A, C, and E may strengthen the patient's immune system. Because large doses of some vitamins can cause **diarrhea** and other serious side effects, they should not be taken without a doctor's approval. Additionally, large doses of vitamins and herbal remedies may interfere with the primary cancer treatment programs. Approval from the treating doctor is imperative.

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Maureen Haggerty

Porfimer sodium

Definition

Porfimer sodium (trade name Photofrin) is a photosensitizing agent that belongs to a group of medicines known as antineoplastics. Porfimer sodium is sometimes called a hematoporphyrin derivative.

Purpose

Porfimer is used in a treatment called photodynamic therapy (PDT). This form of cancer treatment is for patients presenting with obstructing esophageal and endobronchial non-small cell lung cancers (NSCLC) and early stage radiologically occult endobronchial cancer. As of the early 2000s, PDT is considered an experimental treatment for cancer of the esophagus. In 2003, however, the Food and Drug Administration (FDA) added Barrett's esophagus to the list of conditions for which Photofrin is an approved treatment. Some patients with Barrett's esophagus develop precancerous lesions that respond well to treatment with porfimer sodium.

As of 2004, PDT is being studied as a treatment for breast cancer that has progressed to the chest wall. Of one group of 14 patients, nine demonstrated a complete response to PDT.

Another new development is the use of porfimer sodium to treat cancers in the abdominal cavity and the brain. A group of researchers in Boston have used a needle to insert a small-diameter quartz optical fiber that transmits laser light to the pancreas, liver, and spleen to activate the Photofrin. A second team in Salt Lake City has used a new light-delivery device based on light-emitting diode (LED) technology to administer PDT to patients with recurrent brain tumors.

Description

The FDA granted its original approval to porfimer sodium in December 1995. Porfimer is a chemical mixture of up to eight porphyrin units. The freeze-dried compound exists as a dark red to reddish-brown cake or powder and is typically reconstituted with 5% dextrose or 0.9% sodium chloride. Porfimer sodium's antitumor effects are dependent upon its activation by a specific wavelength of light that results in the subsequent release of highly toxic oxygen-free radicals. Additionally, PDT using porfimer produces a significant decrease in blood flow to the treatment area that enhances necrosis in certain tumor cells. Clinical test results suggest that use of porfimer sodium for the palliative management of **esophageal cancer**, and NSCLC yields a statistically significant improvement after a single course of therapy. Porfimer sodium and the associated laser treatment have not been formally tested in conjunction with other photosensitizing compounds. However, it may be speculated that an increase in the photosensitive reaction would result.

Recommended dosage

The dose of porfimer sodium will vary among patients. The oncologist will make a final dose determination based on a number of factors, including body weight. An appropriate starting regimen for adults would be:

- 2mg porfimer per kg of body weight injected into a vein.
- Approximately 48 hours post injection, tumor illumination with a laser light source set at 630nm wavelength.
- Two to three days post tumor illumination, the physician will remove the destroyed cancer cells.
- If prescribed, a second laser treatment may be given 96–120 hours after the initial porfimer injection followed by subsequent removal of destroyed cancer cells.
- Patients may receive a second dose of porfimer at a minimum of 30 days from the initial treatment for up to three cycles, each 30 days apart.

Precautions

All patients who have received PDT must avoid exposure of the skin and eyes to direct sunlight and bright indoor lighting for a minimum of 30 days. In July 2000, the FDA added the following to patient information labeling of Photofrin: "Some patients may remain photosensitive for up to 90 days or more." Sensitivity is produced from the residual porfimer that has not cleared the patient's system; therefore, ambient indoor lighting will help to gradually quench the photosensitive effect. Intermittent exposure trials of a small patch of skin to direct sunlight should be conducted in

10-minute segments beginning 30 days after PDT, and before returning to normal outdoor activities. If no photosensitive reaction (redness, edema, blistering) is apparent 24 hours after exposure, cautious and gradually increased exposure may continue. If the test results are positive, patients should continue precautions for an additional two weeks before repeating the exposure test. Over-the-counter sunscreens are of no use because the photo activation of porfimer occurs in the visible light range. Patient eye sensitivity should be guarded for a minimum of 30 days by wearing dark sunglasses that allow for no greater than 4% of available white light to pass through the lenses. PDT treatment scheduling before or after **radiation therapy** should be properly spaced to avoid any cumulative inflammatory response from one treatment regimen to the next. A two- to four-week recovery phase between treatment types is recommended. Careful monitoring of endobronchial lesion patients is required to reduce the risk of respiratory distress caused by necrotic tissue obstructing the airway. These patients are also at risk from bleeding problems associated with erosion into a major blood vessel. As with all **antineoplastic agents**, pregnancy should be avoided. If the patient is pregnant, PDT should only be used if the potential benefits outweigh the risks to the fetus.

Side effects

Side effects are associated with all antineoplastic drugs, and patients should be instructed to discuss any concerns. Side effects produced with porfimer that may engender patient concern, but do not typically require medical attention, may include mild **diarrhea** or constipation, mild **nausea and vomiting**, blistering, redness or swelling of the skin, difficulty sleeping, weakness, and vision changes. These conditions usually subside as the body adjusts to the porfimer. Side effects associated with porfimer sodium that do require immediate medical attention include:

- shortness of breath or trouble breathing
- fast or irregular heartbeat
- high or low blood pressure
- spitting blood
- severe stomach, abdominal, or chest pain
- chills or fever
- dizziness or fainting
- coughing or wheezing
- unusual weight gain
- excessive fatigue or weakness
- swelling in the face, feet, neck, or lower legs
- white patches in the mouth
- tightness in the chest
- yellow coloration of the eyes or skin

KEY TERMS

Benign growth—A noncancerous cell growth that does not metastasize and does not recur after treatment or removal.

Cancer screening—A procedure designed to detect cancer even though a person has no symptoms, usually performed using an imaging technique.

CT scan—An imaging technique that uses a computer to combine multiple x-ray images into a two-dimensional cross-sectional image.

Electron—One of the small particles that make up an atom. An electron has the same mass and amount of charge as a positron, but the electron has a negative charge.

Gamma ray—A high-energy photon, emitted by radioactive substances.

Half-life—The time required for half of the atoms in a radioactive substance to disintegrate.

Malignant growth— A cell growth or tumor that becomes progressively worse and that can metastasize elsewhere in the body.

Metabolism—The sum of all physical and chemical processes occurring in the body to maintain its integrity and also the transformations by which energy is made available for its uses.

MRI—A special imaging technique used to image internal parts of the body, especially soft tissues.

Photon—A light particle.

Positron—One of the small particles that make up an atom. A positron has the same mass and amount of charge as an electron, but the positron has a positive charge.

Interactions

There have been no formal interaction studies between porfimer and other drugs. One may speculate on the possible synergistic effects of porfimer in conjunction with other photosensitizing agents, such as phenothiazines, chlorpropramide, **demeclocycline**, doxycycline, and tetracycline. Animal research studies suggest certain compounds decrease the effectiveness of porfi-

mer used in PDT. These inhibitors include drug compounds such as dimethyl sulfoxide (DMSO) and ethanol that act by inhibiting the formation of free radicals. Other drug groups, such as thromboxane A_2 inhibitors, inhibit by decreasing clotting, vasoconstriction, or platelet aggregation. Other pre-clinical trial data suggests a decrease in porfimer efficacy in PDT in response to glucocorticoids hormones, calcium channel blockers, and prostagladin synthesis inhibitors. As with any course of treatment, patients should first notify their doctors of any medications they are taking.

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Positron emission tomography

Definition

Positron emission tomography (PET) is a highly specialized imaging technique using short-lived radiolabeled substances to produce powerful images of the body's biological function.

Purpose

Besides being used to investigate the metabolism of normal organs, PET has also become the technique of choice to investigate various neurological diseases and disorders, including stroke, epilepsy, Alzheimer's disease, Parkinson's disease, and Huntington's disease. Various psychiatric disorders, such as schizophrenia, **depression**, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, and Tourette syndrome, are also imaged by PET.

PET is especially useful in the context of cancer because it can detect metastatic tumors that may not be visualized by other imaging techniques. It is also being increasingly used not only as a cancer diagnostic tool, but also to help physicians design the most beneficial therapies. For example, it may be used to assess response to **chemotherapy**. PET imaging is very accurate in differentiating malignant from benign cell growths, and in assessing the spread of malignant tumors. PET is also used to detect recurrent brain tumors and cancers of the lung, colon, breast, lymph nodes, skin, and other organs.

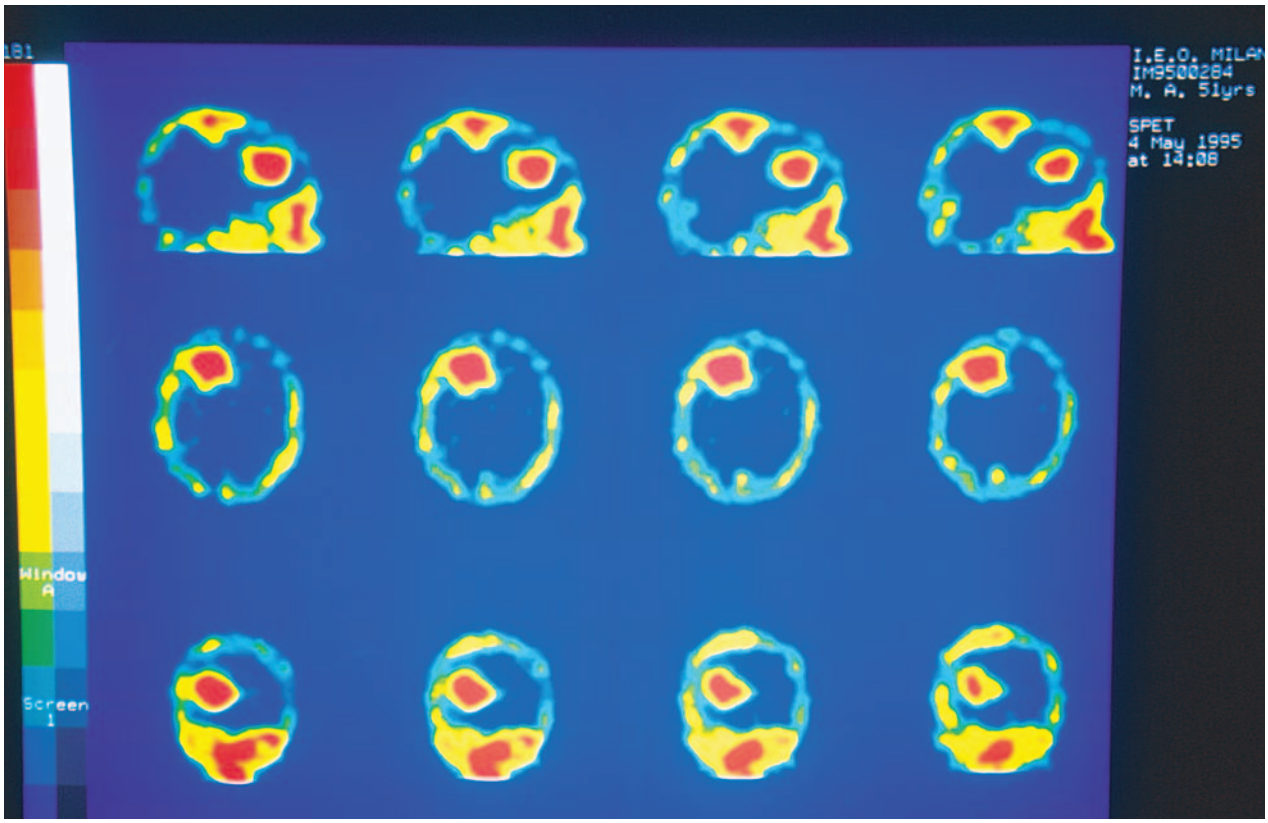
Precautions

In some cases, patients may be allergic to the radioactive agents used for PET. A patient with known allergies should discuss this with his or her specialist before undergoing the PET scan.

Description

PET is used in conjunction with compounds that closely resemble a natural substance used by the body, such as a simple sugar (e.g. glucose), labeled with a radioactive atom and injected into the patient. These compounds (radionuclides or **radiopharmaceuticals**) emit particles called positrons. As positrons emitted from the radionuclides encounter electrons in the body, they produce high-energy photons (gamma rays) that can be recorded as a signal by detectors surrounding the body. The radionuclides move through the body and accumulate in the organs targeted for examination. A computer collects the distribution of radioactivity and reassembles them into actual images.

By further defining a lesion seen on other imaging modalities, PET may enhance assessment of tumors exceedingly well. This is because of its operating principle. The radiolabeled sugars injected into the patient will be used by all body cells, but more sugar will be used by cells that have an increased metabolism. Cancer cells are highly



Positron emission tomography (PET) images of an oncology patient's brain. PET imaging can be used to differentiate between malignant and benign cell growths, assess the spread of malignant tumors, and detect recurrent brain tumors. *(Custom Medical Stock Photo. Reproduced by permission.)*

metabolic, meaning that they use more sugar than healthy nearby cells, and they are easily seen on the PET scan. PET images thus show the chemical functioning of an organ or tissue, unlike **x ray**, computed tomography, or magnetic resonance imaging, which show only body structure.

Preparation

The radiopharmaceutical is given by intravenous injection or inhaled as a gas a few minutes before the PET procedure. How it is administered depends on the radiopharmaceutical used and which one is selected depends on what organ or body part is being scanned. During the scan, the patient lies comfortably; the only discomfort involved may be the pinprick of a needle used to inject the radiopharmaceutical.

Aftercare

No special aftercare measures are indicated for PET.

Risks

Some of radioactive compounds used for PET scanning can persist for a long time in the body. Even though only a small amount is injected each time, the long half-lives of these compounds can limit the number of times a patient can be scanned. However, PET is a relatively safe procedure. PET scans using radioactive fluorine result in patients receiving exposures comparable to (or less than) those from other medical procedures, such as the taking of x rays. Other scanning radiopharmaceuticals—for instance, 6-F-dopa or radioactive water—normally cause even less exposure.

Normal results

The PET scan of a healthy organ or body part will yield images without contrasting regions, because the radiolabeled sugar will have been metabolised at the same rate.

Abnormal results

The PET scan of a diseased organ or body part however, will yield images showing contrasting regions, because the radiolabeled sugar will not have been metabolized at the same rate by the healthy and diseased cells.

QUESTIONS TO ASK THE DOCTOR

- How many PET scans will I have to undergo?
- Are there any risks associated with the radiopharmaceuticals that will be injected?
- How reliable are PET scans for my type of cancer?

See also Imaging studies; Nuclear medicine scans.

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Lisa Christenson
Monique Laberge, Ph.D.

Prednimustine

Definition

Prednimustine is one of a group of antineoplastic (antitumor) drugs known as alkylating agents. As of mid-2001, it is an **investigational drug**.

Purpose

Prednimustine has been used in the treatment of **chronic lymphocytic leukemia**, **non-Hodgkin's lymphomas**, and other malignant conditions including **breast cancer**.

Description

Prednimustine is one of a group of drugs based on the mustard gas used as a weapon in World War I. Like many antineoplastic (antitumor) therapies, prednimustine acts by killing quickly growing cells. Since cancerous cells are generally growing faster than normal cells, drugs that kill quickly growing cells generally affect tumors more than normal cells. However, some normal cells, such as white blood cells and platelets, also grow quickly and can be severely affected by antineoplastic drugs. Antitumor therapies create a situation in which the drug is racing to kill the tumor before it causes irreparable damage to normal tissues. The ideal situation is one in which the growth of the tumor is severely affected, but the growth of normal cells is unaffected. However, not every situation is ideal. Some patients taking antitumor drugs may have to discontinue treatment due to the severity of the drug's side effects.

Prednimustine probably kills rapidly growing cells by modifying cell's DNA with a chemical structure called an alkyl group. Thus, it is included in the group of alkylating agents. Prednimustine is a combination of two drugs joined together: **chlorambucil** (an alkylating agent) and methylprednisolone (a steroid).

Prednimustine is an investigational drug in the United States. This means that the FDA has not approved this drug for marketing in the U.S., as of mid-2001. Generally, investigational drugs are made available through participation in research studies.

Many drugs have toxic side effects, some of which are difficult to detect. **Clinical trials** are used to determine the side effects, drug interactions, and precautions for medicines, as well as their efficacy. Successful completion of multi-step clinical trials results in FDA approval of a drug. Many drugs that are used in clinical trials never gain FDA approval, however, possibly because of severe side effects which outweigh the benefits of the medication, or because the medication does not perform the function for which it was tested. Final approval of a drug is also expensive. Some drugs may not receive the financial support necessary to achieve final approval.

Recommended dosage

Since prednimustine is investigational, there is no recommended dosage. Various dosing schedules have been reported in the literature for different cancers.

Precautions

Patients who take this drug should avoid pregnancy, since this drug may cause fetal abnormalities.

KEY TERM

Investigational drug—A drug that has not been approved for marketing by the FDA. These drugs are generally available to patients through participation in research studies.

Side effects

In the published reports of prednimustine use, the most common side effect is myelosuppression, the damage to white blood cells and platelets. Such damage may result in infection and bleeding, respectively. Steroid side effects, such as fluid retention and high glucose, have also been reported.

Interactions

As of mid-2001, information on the interactions of prednimustine is not available.

See also Chlorambucil.

Michael Zuck, Ph.D.

Prednisone *see* **Corticosteroids**

Pregnancy and cancer

Definition

For the most part, cancer that strikes during a pregnancy is unrelated to the pregnancy. The exception is choriocarcinoma. This cancer is only found in pregnancy.

Description

Pregnancy can be a joyous time for a woman, but when cancer is diagnosed, a tremendous dilemma can arise, both for the woman and for her health care providers. Cancer is not common in pregnancy, and is rarely the cause of maternal mortality. However, in any pregnancy there are always two patients to consider—the mother and the fetus. When a pregnant woman has cancer, the health of the mother may be pitted against the well-being of the fetus. For women who do not have regular medical visits, pregnancy may be a time for regular prenatal visits. For them, screenings done in pregnancy may serve as an opportunity to detect a hidden cancer.

Interestingly, pregnancy also has some protective effects against breast cancer. Studies have firmly established that early full-time pregnancy helps lower risk for breast cancer for a woman's lifetime.

Choriocarcinoma arises from embryonic fetal tissue called the chorion and chorionic villi. It may be associated with a molar pregnancy, an ectopic pregnancy, and may even develop after the delivery of a normal fetus. It may be referred to as gestational trophoblastic disease (GTD), or gestational trophoblastic tumor. A non-malignant form is a hydatiform mole, but the tissue can become cancerous. Vaginal bleeding and high beta human chorionic gonadotropin (hCG) levels characterize the condition.

Ultrasound is effective in evaluating the mass to establish the presence or absence of a fetus and of a fetal heartbeat. The tissue must be evacuated and sent to pathology for evaluation. If cancerous cells are found, **chemotherapy** is begun. Chemotherapy has been shown to be extremely effective in treating choriocarcinoma. If left untreated, choriocarcinoma readily metastasizes, or spreads to other organs.

Incidence of GTD rises with maternal age. Women who desire future pregnancies should discuss this as part of the treatment plan to ensure fertility-sparing choices. Some women normally have high hCG levels. If they have some abnormal vaginal bleeding they can be incorrectly diagnosed as having choriocarcinoma if they have a high hCG level without other evidence of a pregnancy. Before undergoing chemotherapy or surgery, women should have a urine pregnancy test done as well, and/or have blood hCG tests done that are able to discriminate between various forms of hCG. Some laboratory hCG tests have a high false-positive rate, and are not designed to screen for hCG that is associated with cancer.

The most common cancers occurring during pregnancy, in descending order are:

- **Cervical cancer**. About 0.5 to 5.0% of cervical cancers occur in pregnant women, and about one-third of women are under 35 when given the diagnosis. Survival rates for pregnant versus non-pregnant women are similar. It is safe to have a Pap smear during a prenatal visit. Suspicious findings may lead to a colposcopy and **biopsy**. There may be increased bleeding from the biopsy site in the pregnant woman. If cervical cancer is found, the stage of cancer and trimester of pregnancy will determine if immediate surgery is needed or if treatment can be postponed until the fetus matures. With cervical cancer a cesarean delivery will be

recommended, perhaps before full term of 40 weeks if the fetus' lungs are sufficiently mature.

- **Breast cancer**. Breast cancer occurs in about one out of every 3,000 pregnancies. As in non-pregnant women, infiltrating ductal carcinoma is the most prevalent type. When determining the type and stage, the tumor also will be evaluated for being estrogen receptor positive or negative (ER-positive, ER-negative). Pregnancy hormones accelerate the growth of ER-positive tumors. Pregnancy has less of an impact on ER-negative tumors. The pregnancy hormones can alter the test results and increase the number of false negatives of hormone receptor testing. Because of the normal breast changes in pregnancy, it is more difficult to detect a lump when pregnant, so diagnosis may be delayed while the tumor continues to grow. Pregnancy also increases the density of the breast and makes **mammography** less sensitive. Ultrasound can be used to differentiate between a fluid-filled lump and a solid tumor. About 67% of pregnant women with breast cancer have positive lymph nodes versus 38% of non-pregnant women. Studies indicate that about 47% of pregnant women with positive lymph nodes reach five-year survival versus 59% of non-pregnant women with positive nodes. For lactating women, some of the signs of mastitis are similar to the signs of inflammatory breast cancer. The diagnosis of cancer may be delayed because of the confusion. Some studies indicate that if an abscess is drained from a breast with mastitis, a sample should be sent to pathology. Pregnant women may experience bleeding from any procedures done on the breast due to increased vascularity.
- **Melanoma**. The average age for malignant melanoma is 45. About 30–40% of cases appear during the childbearing years. About 8% of women are pregnant at the time of diagnosis. During pregnancy the thickness of the lesion is greater, and nodal metastases more frequently occur. If there has been nodal **metastasis**, survival may be less than three years. Melanoma also can spread to the placenta and to the fetus. However, prognosis for the pregnant woman is greater if she carries to term (66.5% survival at five years), than if the pregnancy is terminated following diagnosis (33.5% survival at five years). Because most lesions appear on the extremities, treatment may begin during the pregnancy.
- Hodgkin's disease. Hodgkin's occurs about one in six thousand pregnancies. The average age for a diagnosis of Hodgkin's is 30. However, the prognosis for the pregnant woman is about the same as for a non-pregnant woman. Signs such as **fever**, **night sweats**, and unexplained **weight loss** indicate a higher stage of disease. A nodal biopsy can safely be done during pregnancy, but pregnancy can alter the test results. Treatment may include a short course of chemotherapy and radiation to the affected nodal area if the fetus can be adequately shielded. If this cannot be done safely, radiation may wait until after delivery. Nodal sclerosis is a common subtype of Hodgkin's and is frequently seen in adolescents and young adults. Non-Hodgkin's lymphoma is usually seen after the childbearing years.
- **Ovarian cancer** is extremely rare during pregnancy; only 1:10,000 to 1:100,000 full term deliveries are cases of this cancer. It is usually low grade and low stage (Stage 1) cancer. Germ cell malignancies are the most common form of ovarian cancer in young women. Germ cell cancer can grow very rapidly, so immediate chemotherapy will be discussed. During pregnancy alpha-fetoprotein levels are tested to check if the fetus may have a neural tube defect. However, this same test is used in the non-pregnant woman as a screening for germ cell cancer. Older women are more prone to epithelial and low malignancy potential ovarian cancers. It may be the prenatal ultrasound that first alerts a woman to her having ovarian cancer. The cancer tumor marker CA-125 is unreliable in pregnancy, as the levels go up during this time. Ovarian tumors may undergo torsion, or twisting, creating extreme pain that may be mistaken for appendicitis or an ectopic pregnancy if gestation is still early.
- Colorectal cancer is the third most common cancer in women, with 67,000 cases in 1999. About 10% of cases occur in patients under the age of 40; only about 2% of cases occur under the age of 30. Early occurrence is linked with high risk. There may be a delay in diagnosis, as some of the symptoms of colorectal cancer overlap symptoms seen in pregnancy. Because of the delay, a higher degree of disease may present at diagnosis. Women considering pregnancy should request screening prior to becoming pregnant. Signs of colorectal cancer include: nausea, abdominal bloating, backache, rectal bleeding, pain, and a change in bowel habits.
- Leukemia is quite rare during pregnancy, occurring in one out of 75,000 pregnancies. During pregnancy, acute myelocytic leukemia is usually the form seen. If treatment is begun right away, the prognosis for the pregnant woman is similar to that of the non-pregnant woman. Complete remission rates are also similar. Untreated, the disease can be rapidly fatal. The woman with leukemia is at greater risk for miscarriage, fetal growth retardation, prematurity and stillbirth.

Causes

As women delay their childbearing years into their forties and even fifties, an increase of cancer during pregnancy is occurring. This is due to the overlap of

KEY TERMS

Cesarean section—This procedure to deliver a baby involves an incision made through the abdominal wall and into the uterus to extract the baby.

Colposcopy—During a colposcopy a practitioner uses a special lighted instrument with magnification lenses (called a colposcope) to clearly visualize and examine the vagina and cervix. This procedure may be done when a Pap smear has come back showing suspicious or abnormal cells. If an area of the vagina or cervix looks suspicious in any way the practitioner may take a sample of tissue, called a biopsy, for further review by a pathologist.

Ectopic pregnancy—A pregnancy that occurs outside the uterus, most commonly in a fallopian tube. Early detection is important to avoid potential rupture of the fallopian tube as the fetus grows.

Hydatiform mole—A hydatiform mole is characterized by a larger-than-normal-for-dates uterus, vaginal bleeding, and the presence of multiple cysts stemming from the degeneration of chorionic villi, the early fetal tissue that imbedded into the uterine lining with placental and embryo implantation.

Interdisciplinary team—A group of health care providers from a variety of specialties that meet as a team to address the various needs of a patient. For a woman with cancer, the team may consist of an obstetrician, gynecologic oncologist, radiologist, neonatologist, social worker, nurse specialists, as well as others specific to the needs of a particular patient.

Microcephaly—Microcephaly is a congenital anomaly in which the head is small in proportion to the body. The brain is also underdeveloped, and there is some mental retardation.

Molar pregnancy—A molar pregnancy may be either complete or partial. In a partial mole, there may be a fetal sac, and even initial fetal heart tones. However, the fetus has multiple anomalies, does not grow properly, and eventually dies. When vaginal bleeding occurs the molar pregnancy is discovered, and needs to be evacuated to avoid retention of the tissue. In a complete mole, the ovum is fertilized but contains no genetic material. The embryo is unable to survive for very long. Complete evacuation of the uterus in necessary to avoid the development of choriocarcinoma.

Teratogenic—A substance or process affecting normal fetal development, leading to congenital malformations. Teratogens include alcohol, certain medications, and radiation.

childbearing with the usual times of occurrence of certain cancers. The exact cause of most cancers is not yet known. However, estrogen is known to play a role in the development of endometrial and ovarian cancers. Research has shown that smoking increases the risk of developing cervical cancer, as well as other cancers.

Special concerns

Decisions need to be made about commencing treatment, or delaying treatment until after the pregnancy is finished. Accurate staging of the tumor will be critical. The woman will be asked if the pregnancy is desired. If not, and if the gestation is less than 24 weeks, therapeutic abortion may be considered. Depending on the type and stage of the cancer, a delay in treatment might not affect the mother's prognosis. Fetal lung maturity may be monitored, so that a safe early delivery can be planned. As the fetus nears term, there is a significant decrease in morbidity and mortality for every extra two weeks it remains in utero.

A pregnant woman with cancer has a great need for an interdisciplinary team of experienced practitioners. Oncologists who have experience with treatment during pregnancy may be able to offer more choices for treating the cancer while maintaining a viable pregnancy. Practitioners also need experience in managing the treatment side effects in a safe way for the fetus. For example, corticosteroid use can increase the incidence of cleft palate, and affect maternal glucose intolerance.

Pregnant women should not take any over-the-counter medication, including herbal supplements, without first consulting their obstetrical provider. Medications and supplements considered safe for a non-pregnant woman may have harmful effects on the fetus.

Treatments

Cancer treatment usually involves some combination of surgery, radiation and chemotherapy. During the first trimester, or the first 12 weeks of gestation, the fetus' organs are developing and are very susceptible to teratogenic substances (substances that affect normal fetal development). When treatment is undertaken, it is most commonly in the second trimester, when early fetal development has already taken place.

When contemplating surgery during pregnancy, the risks for both mother and fetus must be considered. Abdominal surgery poses the greatest risk to the pregnancy, however some women can successfully have an ovary removed and still bring a healthy fetus to term. The removal of the ovary needs to take place after the first trimester, once the placenta has taken over the progesterone hormone production of the corpus luteum. General anesthesia is often chosen for surgery. The safest time for surgery is during the second trimester, but the risk of preterm labor, intrauterine growth retardation, and fetal death still exists. **Mastectomy** is often recommended for the treatment of breast cancer during pregnancy, although breast-conserving surgery may also be an option.

In the first 10 days following conception, radiation may kill the fetus, or may have no effect at all. From 10 days to 14 weeks, a fetus exposed to radiation is at risk for:

- intrauterine growth retardation
- central nervous system (CNS) abnormalities
- microcephaly
- severe mental retardation
- eye anomalies

From eight weeks until term, the fetus is still at risk for CNS abnormalities and milder forms of microcephaly and mental retardation from radiation. If the mother receives high doses of radiation, intrauterine death may occur. Because of the scarcity of research data, the *threshold dose* is unknown. **Childhood cancers**, other cancers later in life, and cancer appearing in later generations are also of concern. Research evaluating the outcome of the children of pregnant women exposed to the atomic bomb in Japan indicates the effects of radiation exposure may show up even five generations later.

When deciding on chemotherapy during pregnancy, several factors are considered:

- which chemotherapy drugs are effective for the woman's particular type of cancer, and of these which are safe for the developing fetus
- the stage of fetal development
- how long the chemotherapy will be administered
- how often it will be administered
- whether the chemotherapeutic agent crosses the placental barrier to the fetus

There are also maternal factors to consider. During pregnancy a woman's blood volume and cardiac output increase, which affects the drugs' concentration levels. If the woman has hyponatremia, this increases the drug concentration in her system. Maternal obesity can affect lipid-soluble drugs. As with radiation, the fetus is most susceptible during the first trimester. Congenital malformations and miscarriage are the most common consequences.

Fortunately, some chemotherapy drugs seem to be well tolerated by the fetus during the second and third trimesters. These drugs include **fluorouracil**, **doxorubicin** (Adriamycin), **bleomycin**, **vinblastine**, **dacarbazine**, and **cyclophosphamide**. Even so, the fetus is at risk for low birthweight, miscarriage, and premature birth. Chemotherapy is rarely administered near term. Treatment at this point may be delayed until after delivery, and during this time period the placenta is less able to effectively excrete the drug(s). Drugs that may not harm the fetus *in utero* may be harmful if consumed via the breast milk. For this reason, breastfeeding is usually discouraged. **Methotrexate** is known to be teratogenic and so is not given in pregnancy. **Daunorubicin** and **cytarabine** are teratogenic in the first trimester. There is not enough known about **paclitaxel** and pregnancy to consider its use. Of additional concern for the pregnant woman receiving treatment for cancer is the effects on the fetus

QUESTIONS TO ASK THE DOCTOR

- What type and stage is my cancer?
- If I were not pregnant how would you treat it?
- Since I am pregnant, how do you suggest treating it?
- What is the expected effect on my baby from the treatment?
- What is my prognosis?
- What part of the treatment can safely wait until after I deliver?
- What side effects can I expect from the treatment?
- What are the risks to me from this treatment?
- How will these treatments be managed?
- What long-term effects will my treatment have on my child?
- What alternative treatments are available to help me?
- Which members of my team are experienced in cancer and pregnancy?

of any medications that may be used to deal with treatment side effects.

Alternative and complementary therapies

A pregnant woman has many limitations on taking medications during pregnancy in order to protect the fetus. Medication that would ordinarily be available to deal with the side effects of cancer treatment may be harmful to the fetus. A helpful resource on the patient's interdisciplinary team is a practitioner with experience in the safe use of complementary therapies for cancer during pregnancy. Mind/body techniques such as guided imagery and meditation can help decrease some of the stress of this time. Acupuncture has been shown to be effective in dealing with the nausea associated with chemotherapy. Support groups can also be a great source of strength and information.

See also Fertility issues.

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Cancer Research Institute. 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

The Gilda Radner Familial Ovarian Cancer Registry. Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263-0001. (800) 682-7426. <http://www.ovariancancer.com>.

National Cancer Institute. Building 31, Room 10A31, 31 Center Dr., MSC 2580, Bethesda, MD 20892-2580. (301) 435-3848. <http://www.nci.nih.gov>.

National Cancer Institute Cancer Trials Web Site. <http://cancertrials.nci.nih.gov/system>. <http://www.cancertrials.com>.

National Center for Complementary and Alternative Medicine. NCCAM Clearinghouse, PO Box 8218, Silver Spring, MD 20907-8218. (888) 644-6226. <http://nccam.nih.gov>.

Oncolink at the University of Pennsylvania. <http://www.oncolink.upenn.edu>.

Women's Cancer Network. c/o Gynecologic Cancer Foundation, 401 N. Michigan Ave., Chicago, IL 60611. (312) 644-6610. <http://www.wcn.org>.

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Teresa G. Odle

Primary site

Definition

The area in which a cancer originates in the body. Once cancer spreads (metastasizes), the new tumors are called secondary tumors, or metastases.

Kate Kretschmann

Procarbazine

Definition

Procarbazine is an anticancer agent that kills cancer cells, also known by the brand name Matulane. It has received approval by the Food and Drug Administration (FDA) for the treatment of advanced **Hodgkin's disease** in combination with other anticancer drugs.

Purpose

Procarbazine is used in the treatment of various cancers, although the best established usage is with Hodgkin's disease. Other cancers in which procarbazine is sometimes used include other lymphomas, brain tumors, skin cancer, lung cancer, and **multiple myeloma**.

Description

Procarbazine is a cytotoxic drug, which means that it kills cancer cells. Procarbazine works by interfering with way the DNA and RNA in cells produce proteins by binding to it in the cells.

KEY TERMS

Cytotoxic drug—An anticancer drug that acts by killing or preventing the division of cells.

DNA (deoxyribonucleic acid)—An acid found in all living cells that contains tiny bits of genetic information.

Platelets—Components of the blood involved in clotting.

RNA (ribonucleic acid)—The tiny substances that transmit messages in the DNA to other elements in the cell.

Recommended dosage

Procarbazine is often given at a dose of 60 to 100 mg per square meter of body surface area for ten to fourteen days of each course of therapy. In addition, patients who have had pre-existing problems with liver, kidney, or bone marrow function may receive reduced doses.

Precautions

While on therapy with procarbazine, patients should not drink alcohol because it may interact with the drug to cause a flushed and hot sensation. Certain foods such as chocolate, fava beans, imported beer, Chianti wines, and ripe cheeses (camembert, cheddar, emmenthaler, stilton), caviar, pickled herring, fermented sausages (bologna, pepperoni, salami, summer sausage), should be avoided as they may cause a dangerous increase in blood pressure if eaten while receiving procarbazine.

Side effects

A carefully monitored side effect of procarbazine is a decrease in the white blood cells that fight infection and the platelet cells that prevent bleeding. The most severe side effect is **nausea and vomiting**. Patients should adhere to the antiemetic regimen prescribed for them to prevent this side effect. There may be neurologic side effects such as confusion, sleepiness, **depression**, nightmares, agitation, and nervousness. Patients may have reproductive dysfunction.

Interactions

Procarbazine has numerous drug interactions. Therefore, it is important that patients alert their physicians to all medications they are taking (prescription, over-the-counter, or herbal) prior to starting treatment with procarbazine or any other drug.

Bob Kirsch

Prochlorperazine *see* **Antiemetics**

Promethazine *see* **Antiemetics**

Prostate cancer

Definition

Prostate cancer is a disease in which cells in the prostate gland become abnormal and start to grow uncontrollably, forming tumors.

Description

Prostate cancer is a malignancy of one of the major male sex glands. Along with the testicles and the seminal vesicles, the prostate secretes the fluid that makes up semen. The prostate is about the size of a walnut and lies just behind the urinary bladder. A tumor in the prostate interferes with proper control of the bladder and normal sexual functioning. Often the first symptom of prostate cancer is difficulty in urinating. However, because a very common, non-cancerous condition of the prostate, benign prostatic hyperplasia (BPH), also causes the same problem, difficulty in urination is not necessarily due to cancer.

Cancerous cells within the prostate itself are generally not deadly on their own. However, as the tumor grows, some of the cells break off and spread to other parts of the body through the lymph or the blood, a process known as **metastasis**. The most common sites for prostate cancer to metastasize are the seminal vesicles, the lymph nodes, the lungs, and various bones around the hips and the pelvic region. The effects of these new tumors are what can cause death.

Demographics

Prostate cancer is the most commonly diagnosed malignancy among adult males in Western countries. Although prostate cancer is often very slow growing, it can be aggressive, especially in younger men. Given its slow growing nature, many men with the disease die of other causes rather than from the cancer itself.

Prostate cancer affects African-American men twice as often as white men; the mortality rate among African-

Americans is also two times higher. African-Americans have the highest rate of prostate cancer of any world population group.

Causes and symptoms

The precise cause of prostate cancer is not known. However, there are several known risk factors for disease including age over 55, African-American heritage, a family history of the disease, occupational exposure to cadmium or rubber, and a high-fat diet. Men with high plasma **testosterone** levels may also have an increased risk for developing prostate cancer.

Frequently, prostate cancer has no symptoms and the disease is diagnosed when the patient goes for a routine screening examination. However, when the tumor is big or the cancer has spread to the nearby tissues, the following symptoms may be seen:

- weak or interrupted flow of the urine
- frequent urination (especially at night)
- difficulty starting urination
- inability to urinate
- pain or burning sensation when urinating
- blood in the urine
- persistent pain in lower back, hips, or thighs (bone pain)
- painful ejaculation

Diagnosis

Prostate cancer is curable when detected early. Yet the early stages of prostate cancer are often asymptomatic, so the disease often goes undetected until the patient has a routine physical examination. Diagnosis of prostate cancer can be made using some or all of the following tests.

Digital rectal examination (DRE)

In order to perform this test, the doctor puts a gloved and lubricated finger (digit) into the rectum to feel for any lumps in the prostate. The rectum lies just behind the prostate gland, and a majority of prostate tumors begin in the posterior region of the prostate. If the doctor does detect an abnormality, he or she may order more tests in order to confirm these findings.

Blood tests

Blood tests are used to measure the amounts of certain protein markers, such as prostate-specific antigen (PSA), found circulating in the blood. The cells lining the prostate generally make this protein and a small amount can be detected normally in the bloodstream. In contrast, prostate cancers produce a lot of this protein, significantly raising the circulating levels. A finding of a PSA level higher than normal for the patient's age group therefore suggests that cancer is present.

Transrectal ultrasound

A small probe is placed in the rectum and sound waves are released from the probe. These sound waves bounce off the prostate tissue and an image is created. Since normal prostate tissue and prostate tumors reflect the sound waves differently, the test is an efficient and accurate way to detect tumors. Though the insertion of the probe into the rectum may be slightly uncomfortable, the procedure is generally painless and only takes 20 minutes.

Prostate biopsy

If cancer is suspected from the results of any of the above tests, the doctor will remove a small piece of prostate tissue with a hollow needle. This sample is then checked under the microscope for the presence of cancerous cells. Prostate **biopsy** is the most definitive diagnostic tool for prostate cancer, and this procedure is done quickly and with little pain or discomfort.

Prostate cancer can also be diagnosed based on the examination of the tissue removed during a transurethral resection of the prostate (TURP). This procedure is performed to help alleviate the symptoms of BPH, a benign enlargement of the prostate. Like a biopsy, this is a definitive diagnostic method for prostate cancer.

X rays and imaging techniques

A chest **x ray** may be ordered to determine whether the cancer has spread to the lungs. Imaging techniques (such as **computed tomography** (CT) scans and **magnetic resonance imaging** (MRI)), where a computer is used to generate a detailed picture of the prostate and areas nearby, may be done to get a clearer view of the internal organs. A bone scan may be used to check whether the cancer has spread to the bone.

Treatment team

Prostate cancer is often treated by a team of specialists including a urologist (who may or may not perform surgery), a surgeon (if surgical treatment is used and it is not performed by the urologist), a medical oncologist, and, if **radiation therapy** is used, a radiation oncologist.

Clinical staging, treatments, and prognosis

Once cancer is detected during the microscopic examination of the prostate tissue during a biopsy or TURP, doctors will determine two different numerical scores that will help define the patient's treatment and prognosis.

Tumor grading

Initially, the pathologist will grade the tumor based on his or her examination of the biopsy tissue. The pathologist scores the appearance of the biopsy sample using the Gleason system. This system uses a scale of one to five based on the sample's similarity or dissimilarity to normal prostate tissue. If the tissue is very similar to normal tissue, it is still well differentiated and given a low grading number, such as one or two. As the tissue becomes more and more abnormal (less and less differentiated), the grading number increases, up to five. Less differentiated tissue is considered more aggressive and more likely to be the source of metastases.

The Gleason grading system is best predictive of the prognosis of a patient if the pathologist gives two scores to a particular sample—a primary and a secondary pattern. The two numbers are then added together and that is the Gleason score reported to the patient. Thus, the lowest Gleason score available is two (a primary and secondary pattern score of one each). A typical Gleason score is five (which can be a primary score of two and a secondary score of three or visa-versa). The highest score available is 10, with a pure pattern of very undifferentiated tissue, that is, of grade five. The higher the score, the more abnormal behavior of the tissue, the greater the chance for metastases, and the more serious the prognosis after surgical treatment. A study found that the ten-year cancer survival rate without evidence of disease for grade two, three, and four cancers is 94% of patients. The rate is 91% for grade five cancers, 78% for grade six, 46% for grade seven, and 23% for grade eight, nine, and ten cancers.

Cancer staging

The second numeric score determined by the doctor will be the stage of the cancer, which takes into account the grade of the tumor determined by the pathologist. Based on the recommendations of the American Joint Committee on Cancer (AJCC), two kinds of data are used for staging prostate cancer. Clinical data is based on the external symptoms of the cancer, while histopathological data is based on surgical removal of the prostate and examination of its tissues. Clinical data is most useful to make treatment decisions, while pathological data is the best predictor of prognosis. For this reason, the staging of prostate cancer takes into account both clinical and histopathologic information. Specifically, doctors look at tumor size (T), lymph node involvement (N), the presence of visceral (internal organ) involvement (metastasis = M), and the grade of the tumor (G).

The classification of tumor as T1 means the cancer that is confined to the prostate gland and the tumor that is too small to be felt during a DRE. T1 tumors are often found after examination of tissue removed during a TURP. The T1 definition is subdivided into those cancers that show less than 5% cancerous cells in the tissue sample (T1a) or more than 5% cancerous cells in the tissue sample (T1b). T1c means that the biopsy was performed based on an elevated PSA result. The second tumor classification is T2, where the tumor is large enough to be felt during the DRE. T2a indicates that only the left or the right side of the gland is involved, while T2b means both sides of the prostate gland has tumor.

With a T3 tumor, the cancer has spread to the connective tissue near the prostate (T3a) or to the seminal vesicles as well (T3b). T4 indicates that cancer has spread within the pelvis to tissue next to the prostate such as the bladder's sphincter, the rectum, or the wall of the pelvis. Prostate cancer tends to spread next into the regional lymph nodes of the pelvis, indicated as N1. Prostate cancer is said to be at the M1 stage when it has metastasized outside the pelvis in distant lymph nodes (M1a), bone (M1b) or organs such as the liver or the brain (M1c). Pain, **weight loss**, and **fatigue** often accompany the M1 stage.

The grade of the tumor (G) can be assessed during a biopsy, TURP surgery, or after removal of the prostate. There are three grades recognized: G1, G2, and G3, indicating the tumor is well, moderately, or poorly differentiated, respectively. The G, LN, M descriptions are combined with the T definition to determine the stage of the prostate cancer.

- Stage I prostate cancer comprises patients who are T1a, N0, M0, G1.
- Stage II includes a variety of condition combinations including T1a, N0, M0, G2, 3 or 4; T1b, N0, M0, Any G; T1c, N0, M0, Any G; T1, N0, M0, Any G or T2, N0, M0, Any G.
- Stage III prostate cancer occurs when conditions are T3, N0, M0, any G.
- Stage IV is T4, N0, M0, any G; any T, N1, M0, any G; or any T, any N, M1, Any G.

Prognosis

The prognosis for cancers at Stages I and II is very good. For men treated with stage I or stage II disease, over 95% are alive after five years. Although the cancers

of Stage III are more advanced, the five-year prognosis is still good, with 70% of men diagnosed at this stage still living. The spread of the cancer into the pelvis (T4), lymph (N1), or distant locations (M1) are very significant events, as the five-year survival rate drops to 30% for Stage IV.

Treatment options

The doctor and the patient will decide on the treatment mode after considering many factors. For example, the patient's age, the stage of the disease, his general health, and the presence of any co-existing illnesses have to be considered. In addition, the patient's personal preferences and the risks and benefits of each treatment protocol are also taken into account before any decision is made.

SURGERY For stage I and stage II prostate cancer, surgery is the most common method of treatment because it theoretically offers the chance of completely removing the cancer from the body. Radical **prostatectomy** involves complete removal of the prostate. The surgery can be done using a perineal approach, where the incision is made between the scrotum and the anus, or using a retropubic approach, where the incision is made in the lower abdomen. Perineal approach is also known as nerve-sparing prostatectomy, as it is thought to reduce the effect on the nerves and thus reduce the side effects of impotence and **incontinence**. However, the retropubic approach allows for the simultaneous removal of the pelvic lymph nodes, which can give important pathological information about the tumor spread.

The drawback to surgical treatment for early prostate cancer is the significant risk of side effects that impact the quality of life of the patient. Even using nerve-sparing techniques, studies by the National Cancer Institute (NCI) found that 60% to 80% of men treated with radical prostatectomy reported themselves as impotent (unable to achieve an erection sufficient for sexual intercourse) two years after surgery. This side effect can be sometimes countered by prescribing sildenafil citrate (Viagra). Furthermore, 8% to 10% of patients were incontinent in that time span. Despite the side effects, the majority of men were reported as satisfied with their treatment choice. Additionally, there is some evidence that the skill and the experience of the surgeon are central factors in the ultimate side effects seen.

A second method of surgical treatment of prostate cancer is cryosurgery, or cryotherapy. Guided by ultrasound, surgeons insert up to eight cryoprobes through the skin and into close proximity with the tumor. Liquid nitrogen (temperature of -320.8 degrees F, or -196 C) is circulated through the probe, freezing the tumor tissue. In prostate surgery, a warming tube is also used to keep the urethra from freezing. Patients currently spend a day or two in the hospital following the surgery, but it could be an outpatient procedure in the near future. Recovery time is about one week. Side effects have been reduced in recent years, although impotence still affects almost all who have had cryosurgery for prostate cancer. Cryosurgery is considered a good alternative for those too old or sick to have traditional surgery or radiation treatments or when these more traditional treatments are unsuccessful. There is limited amount of information about the long-term efficacy of this treatment for prostate cancer.

RADIATION THERAPY Radiation therapy involves the use of high-energy x rays to kill cancer cells or to shrink tumors. It can be used instead of surgery for stage I and II cancer. The radiation can either be administered from a machine outside the body (external beam radiation), or small radioactive pellets can be implanted in the prostate gland in the area surrounding the tumor, called brachytherapy or interstitial implantation. Pellets containing radioactive iodine (I-125), palladium (Pd 103), or iridium (Ir 192) can be implanted on an outpatient basis, where they remain permanently. The radioactive effect of the seeds last only about a year.

The side effects of radiation can include inflammation of the bladder, rectum, and small intestine as well as disorders of blood clotting (coagulopathies). Impotence and incontinence are often delayed side effects of the treatment. A study indicated that bowel control problems were more likely after radiation therapy when compared to surgery, but impotence and incontinence were more likely after surgical treatment. Long-term results with radiation therapy are dependent on stage. A review of almost 1,000 patients treated with megavoltage irradiation showed 10-year survival rates to be significantly different by T-stage: T1 (79%), T2 (66%), T3 (55%), and T4 (22%). There does not appear to be a large difference in survival between external beam or interstitial treatments.

HORMONE THERAPY Hormone therapy is commonly used when the cancer is in an advanced stage and has spread to other parts of the body, such as stage III or stage IV. Prostate cells need the male hormone testosterone to grow. Decreasing the levels of this hormone or inhibiting its activity will cause the cancer to shrink. Hormone levels can be decreased in several ways. **Orchiectomy** is a surgical procedure that involves complete removal of the testicles, leading to a decrease in the levels of testosterone. Another method tricks the body by administering the female hormone estrogen. When estrogen is given, the body senses the presence of a sex hormone and stops making the male hormone testosterone. However, there are some unpleasant side effects to hormone therapy. Men may have "hot flashes," enlarge-

ment and tenderness of the breasts, or impotence and loss of sexual desire, as well as blood clots, heart attacks, and strokes, depending on the dose of estrogen. Another side effect is osteoporosis, or loss of bone mass leading to brittle and easily fractured bones.

WATCHFUL WAITING Watchful waiting means no immediate treatment is recommended, but doctors keep the patient under careful observation. This is often done using periodic PSA tests. This option is generally used in older patients when the tumor is not very aggressive and the patients have other, more life-threatening, illnesses. Prostate cancer in older men tends to be slow-growing. Therefore, the risk of the patient dying from prostate cancer, rather than from other causes, is relatively small.

Alternative and complementary therapies

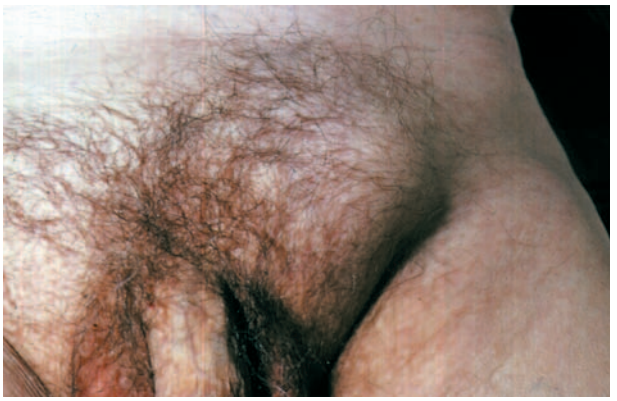
Alternative treatments that have been found helpful in coping with the emotional stress associated with prostate cancer include meditation, guided imagery, and relaxation techniques. Acupuncture is effective in relieving pain in some patients.

A variety of herbal products have been used to treat prostate cancer, including various compounds used in traditional Chinese medicine as well as single agents like Reishi mushrooms (*Ganoderma lucidum*). One herbal compound that was under investigation by the National Center for Complementary and Alternative Medicine (NCCAM) as a possible treatment for prostate cancer was PC-SPES, a mixture of eight herbs adapted from traditional Chinese medicine. In the summer of 2002, however, NCCAM put its studies of PC-SPES on hold when the Food and Drug Administration (FDA) determined that samples of the product were contaminated with undeclared prescription drug ingredients. PC-SPES was withdrawn from the American market in late 2002.

Coping with cancer treatment

The treatment process for prostate cancer can be a physically and emotionally exhausting time. Here are six general suggestions that can help make the process easier. Patients should:

- put their faith and trust in their doctors once a treatment course has been chosen
- remember that a patient is never without power and rights during the course of treatment
- put practical affairs in order
- closely monitor each step of the treatment
- keep close family and friends informed and delegate responsibilities as necessary
- work to make visits pleasant and comfortable



This patient's prostate cancer has metastasized, swelling the lymph nodes in the left groin. *(Photograph by Dr. P. Marazzi. Photo Researchers, Inc. Reproduced by permission.)*

- be careful to eat, sleep, exercise, and conduct daily activities in a healthy manner

Clinical trials

Patients with extraprostatic disease are suitable candidates for **clinical trials**. One trial is the testing of a vaccine (GVAX) that causes the body to mount an **immune response** against all prostate cells. As the prostate is a nonessential organ, the destruction of the normal cells with the tumor cells is not a problem. The vaccine was made using cancer cells from a tumor that had been genetically engineered to express granulocyte/macrophage colony-stimulating factor (GM-CSF), a potent activator of the entire immune system. The additional protein jumpstarted the immune response against the prostate cells upon vaccination and resulted in antitumor immune response.

Other trials for prostate cancer include evaluation of combination therapies, such as postoperative radiation delivery, use of cytotoxic agents, and hormonal treatment using luteinizing hormone-releasing hormone (LHRH) agonists and/or **antiandrogens** to shut down the growth of the hormone-dependent tumors. Other drugs that are being tested as of 2003 are chemoprotective agents like amifostine (Ethyol), which are given to prostate cancer patients to counteract the harmful side effects of radiation treatment.

Prevention

Because the cause of the cancer is not known, there is no definite way to prevent prostate cancer. Given its common occurrence and the low cost of screening, the American Cancer Society (ACS) and the National Comprehensive Cancer Network (NCCN) recommends that all men over age 40 have an annual rectal exam and that men

KEY TERMS

Antiandrogen—A substance that blocks the action of androgens, the hormones responsible for male characteristics. Used to treat prostate cancers that require male hormones for growth.

Benign Prostate Hyperplasia (BPH)—A non-cancerous swelling of the prostate.

Brachytherapy—A method of treating cancers, such as prostate cancer, involving the implantation near the tumor of radioactive seeds.

Gleason Grading System—A method of predicting the tendency of a tumor in the prostate to metastasize based on how similar the tumor is to normal prostate tissue.

Granulocyte/macrophage colony stimulating factor (GM-CSF)—Also known as sargramostim, a substance produced by cells of the immune system that stimulates the attack upon foreign cells. Used to treat prostate cancers as a genetically engineered component of a vaccine that stimulates the body to attack prostate tissue.

Histopathology—The study of diseased tissues at a minute (microscopic) level.

Luteinizing hormone releasing hormone (LHRH) agonist—A substance that blocks the action of LHRH, a hormone that stimulates the production of testosterone (a male hormone) in men. Used to treat prostate cancers that require testosterone for growth.

Orchiectomy—Surgical removal of the testes that eliminates the production of testosterone to treat prostate cancer.

Prostate-Specific Antigen—A protein made by the cells of the prostate that is increased by both BPH and prostate cancer.

Radical Prostatectomy—Surgical removal of the entire prostate, a common method of treating prostate cancer.

Transurethral resection of the prostate (TURP)—Surgical removal of a portion of the prostate through the urethra, a method of treating the symptoms of an enlarged prostate, whether from BPH or cancer.

have an annual PSA test beginning at age 50. African-American men and men with a family history of prostate cancer, who have a higher than average risk, should begin annual PSA testing even earlier, starting at age 45.

QUESTIONS TO ASK THE DOCTOR

- How do my age, general health, and other medical conditions affect my treatment choices?
- What are the T, N, and M stages of my cancer and how do they influence my treatment options?
- How do the Gleason score of my cancer and my blood prostate-specific antigen (PSA) level predict my outlook for survival and affect treatment options?
- What are the likely side effects of each proposed therapy and how will they affect my quality of life?
- What can be done to help manage the side effects of treatment?

However, mandatory screening for prostate cancer is controversial. Because the cancer is so slow growing, and the side effects of the treatment can have significant impact on patient quality of life, some medical organizations question the wisdom of yearly exams. Some organizations have even noted that the effect of screening is discovering the cancer at an early stage when it may never grow to have any outward effect on the patient during this lifetime. Nevertheless, the NCI reports that the current aggressive screening methods have achieved a reduction in the death rate of prostate cancer of about 2.3% for African-Americans and about 4.6% for Caucasians since the mid-1990s, with a 20% increase in overall survival rate during that period.

A low-fat diet may slow the progression of prostate cancer. To reduce the risk or progression of prostate cancer, the American Cancer Society recommends a diet rich in fruits, vegetables and dietary fiber, and low in red meat and saturated fats.

Special concerns

The availability of an early detection system for prostate cancer with the development of the PSA serum test has complicated the treatment of this disease. Early detection of an often slow-growing cancer, where treatment can significantly impact the quality of life of the patient, can be complicated. Long-term studies are currently in progress that should provide the first real quantitative information about the relative efficacy of the different treatment options, the actual occurrence of side effects, and the comparative benefits of watchful

waiting treatment compared with more aggressive action.

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ORGANIZATIONS

The Association for the Cure of Cancer of the Prostate (CaPCure). 1250 Fourth St., Suite 360, Santa Monica, CA 90401. (800) 757-CURE. <http://www.capcure.org>.

National Cancer Institute. Building 31, Room 10A31 31 Center Drive, MSC 2580, Bethesda, MD 20892-2580. (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

National Center for Complementary and Alternative Medicine (NCCAM) Clearinghouse. P. O. Box 7923, Gaithersburg, MD 20898. (888) 644-6226. <http://nccam.nih.gov>.

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Prostatectomy

Definition

Prostatectomy is surgical removal of part of the prostate gland (transurethral resection, a procedure performed to relieve urinary symptoms caused by benign enlargement), or all of the prostate (radical prostatectomy, the curative surgery most often used to treat **prostate cancer**).

Purpose

Benign disease

When men reach their mid-40s, the prostate gland begins to enlarge. This condition, benign prostatic hyperplasia (BPH) is present in more than half of men in their 60s and as many as 90% of those over 90. Because the prostate surrounds the urethra, the tube leading urine from the bladder out of the body, the enlarging prostate narrows this passage and makes urination difficult. The bladder does not empty completely each time a man urinates, and, as a result, he must urinate with greater frequency, night and day. In time, the bladder can overfill, and urine escapes from the urethra, resulting in **incontinence**. An operation called transurethral resection of the

prostate (TURP) relieves symptoms of BPH by removing the prostate tissue that is blocking the urethra. No incision is needed. Instead a tube (retroscope) is passed through the penis to the level of the prostate, and tissue is either removed or destroyed, so that urine can freely pass from the body.

Malignant disease

Prostate cancer is the single most common form of non-skin cancer in the United States and the most common cancer in men over 50. Half of men over 70 and almost all men over the age of 90 have prostate cancer, and the American Cancer Society estimates that 198,000 new cases will be diagnosed in a given year. This condition does not always require surgery. In fact, many elderly men adopt a policy of "watchful waiting," especially if their cancer is growing slowly. Younger men often elect to have their prostate gland totally removed along with the cancer it contains—an operation called radical prostatectomy. The two main types of this surgery, radical retropubic prostatectomy and radical perineal prostatectomy, are performed only on patients whose cancer is limited to the prostate. If cancer has broken out of the capsule surrounding the prostate gland and spread in the area or to distant sites, removing the prostate will not prevent the remaining cancer from growing and spreading throughout the body.

Precautions

Potential complications of TURP include bleeding, infection, and reactions to general or regional anesthesia. About one man in five will need to have the operation again within 10 years.

Open (incisional) prostatectomy for cancer should not be done if the cancer has spread beyond the prostate, as serious side effects may occur without the benefit of removing all the cancer. If the bladder is retaining urine, it is necessary to insert a catheter before starting surgery. Patients should be in the best possible general condition before radical prostatectomy. Before surgery, the bladder is inspected using an instrument called a cystoscope to help determine the best surgical technique to use, and to rule out other local problems.

Description

TURP

This procedure does not require an abdominal incision. With the patient under either general or spinal anesthesia, a cutting instrument or heated wire loop is inserted to remove as much prostate tissue as possible and seal blood vessels. The excised tissue is washed into the bladder, then flushed out at the end of the operation. A catheter is left in the bladder for one to five days to drain urine and blood. Advanced laser technology enables surgeons to safely and effectively burn off excess prostate tissue blocking the bladder opening with fewer of the early and late complications associated with other forms of prostate surgery. This procedure can be performed on an outpatient basis, but urinary symptoms do not improve until swelling subsides several weeks after surgery.

Radical prostatectomy

RADICAL RETROPUBIC PROSTATECTOMY This is a useful approach if the prostate is very large, or cancer is suspected. With the patient under general or spinal anesthesia or an epidural, a horizontal incision is made in the center of the lower abdomen. Some surgeons begin the operation by removing pelvic lymph nodes to determine whether cancer has invaded them, but recent findings suggest there is no need to sample them in patients whose likelihood of lymph node metastases is less than 18%. A doctor who removes the lymph nodes for examination will not continue the operation if they contain cancer cells, because the surgery will not cure the patient. Other surgeons remove the prostate gland before examining the lymph nodes. A tube (catheter) inserted into the penis to drain fluid from the body is left in place for 14–21 days.

Originally, this operation also removed a thin rim of bladder tissue in the area of the urethral sphincter—a muscular structure that keeps urine from escaping from the bladder. In addition, the nerves supplying the penis often were damaged, and many men found themselves impotent (unable to achieve erections) after prostatectomy. A newer surgical method called potency-sparing radical prostatectomy preserves sexual potency in 75% of patients and fewer than 5% become incontinent following this procedure.

RADICAL PERINEAL PROSTATECTOMY This procedure is just as curative as radical retropubic prostatectomy but is performed less often because it does not allow the surgeon to spare the nerves associated with erection or, because the incision is made above the rectum and below the scrotum, to remove lymph nodes. Radical perineal prostatectomy is sometimes used when the cancer is limited to the prostate and there is no need to spare nerves or when the patient's health might be compromised by the longer procedure. The perineal operation is less invasive than retropubic prostatectomy. Some parts of the prostate can be seen better, and blood loss is limited. The absence of an abdominal incision allows patients to recover more rapidly. Many urologic surgeons have not been trained to perform this procedure.

Radical prostatectomy procedures last one to four hours, with radical perineal prostatectomy taking less time than radical retropubic prostatectomy. The patient remains in the hospital three to five days following surgery and can return to work in three to five weeks. Ongoing research indicates that laparoscopic radical prostatectomy may be as effective as open surgery in treatment of early-stage disease.

Cryosurgery

Also called **cryotherapy** or cryoablation, this minimally invasive procedure uses very low temperatures to freeze and destroy cancer cells in and around the prostate gland. A catheter circulates warm fluid through the urethra to protect it from the cold. When used in connection with ultrasound imaging, cryosurgery permits very precise tissue destruction. Traditionally used only in patients whose cancer had not responded to radiation, but now approved by Medicare as a primary treatment for prostate cancer, cryosurgery can safely be performed on older men, on patients who are not in good enough general health to undergo radical prostatectomy, or to treat recurrent disease. Recent studies have shown that total cryosurgery, which destroys the prostate, is at least as effective as radical prostatectomy without the trauma of major surgery.

Preparation

As with any type of major surgery done under general anesthesia, the patient should be in optimal condition. Most patients having prostatectomy are in the age range when cardiovascular problems are frequent, making it especially important to be sure that the heart is beating strongly, and that the patient is not retaining too much fluid. Because long-standing prostate disease may cause kidney problems from urine "backing up," it also is necessary to be sure that the kidneys are working properly. If not, a period of catheter drainage may be necessary before doing the surgery.

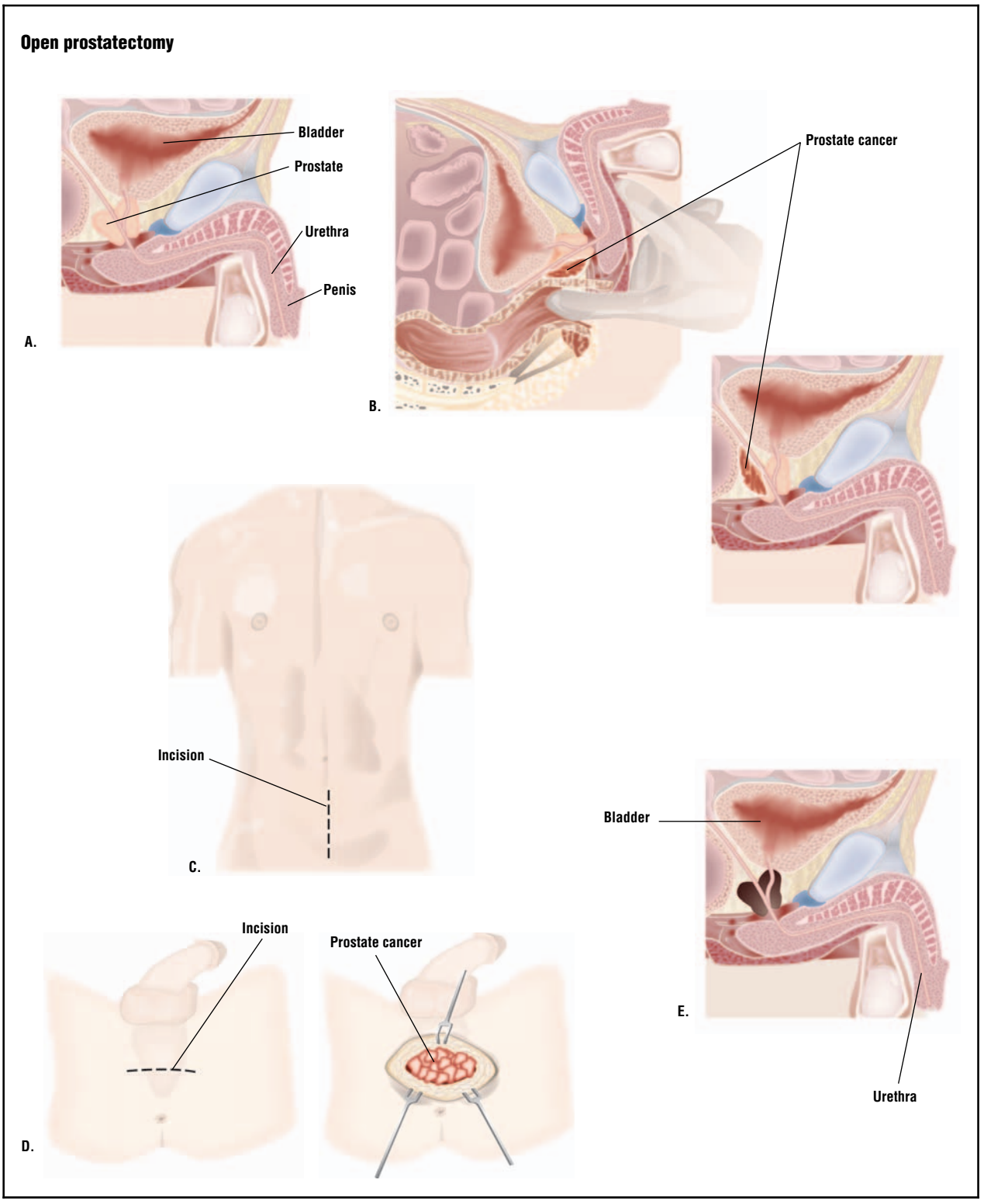
Aftercare

Following TURP, a catheter is placed in the bladder to drain urine and remains in place for two to three days. A solution is used to irrigate the bladder and urethra until the urine is clear of blood, usually within 48 hours after surgery. Whether **antibiotics** should be routinely given remains an open question. Catheter drainage also is used after open prostatectomy. The bladder is irrigated only if blood clots block the flow of urine through the catheter. Patients are given intravenous fluids for the first 24 hours, to ensure good urine flow. Patients resting in bed for long periods are prone to blood clots in their legs (which can pass to the lungs and cause serious breathing problems). This can be prevented by elastic stockings and by periodically exercising the patient's legs. The patient remains in the hospital one to two days following surgery and can return to work in one to two weeks.

Risks

The complications and side effects that may occur during and after prostatectomy include:

- Excessive bleeding, which in rare cases may require blood transfusion.
- Incontinence when, during retropubic prostatectomy, the muscular valve (sphincter) that keeps urine in the bladder is damaged. Less common today, when care is taken not to injure the sphincter.
- Impotence, occurring when nerves to the penis are injured during the retropubic operation. Today's "nerve-sparing" technique has drastically cut down on this problem.
- Some patients who receive a large volume of irrigating fluid after TURP develop high blood pressure, vomiting, trouble with their vision, and mental confusion. This condition is caused by a low salt level in the blood, and is reversed by giving salt solution.
- A permanent narrowing of the urethra called a stricture occasionally develops when the urethra is damaged during TURP.



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KEY TERMS

BPH—Benign prostatic hypertrophy, a very common noncancerous cause of prostatic enlargement in older men.

Catheter—A tube that is placed through the urethra into the bladder in order to provide free drainage of urine and blood following either TUR or open prostatectomy.

Cryosurgery—In prostatectomy, the use of a very low-temperature probe to freeze and thereby destroy prostatic tissue.

Impotence—The inability to achieve and sustain penile erections.

Incontinence—The inability to retain urine in the bladder until a person is ready to urinate voluntarily.

Prostate gland—The gland surrounding the male urethra just below the base of the bladder. It secretes a fluid that constitutes a major portion of the semen.

Urethra—The tube running from the bladder to the tip of the penis that provides a passage for eliminating urine from the body.

- There is about a 34% chance that the cancer will recur within 10 years of the procedure. In addition, about 25% of patients experience what is known as biochemical recurrence, which means that the level of prostate-specific antigen (PSA) in the patient's blood serum begins to rise rapidly. Recurrence of the tumor or biochemical recurrence can be treated with radiation therapy or androgen deprivation therapy.

Normal results

In patients with BPH who have the TURP operation, urination should become much easier and less frequent, and dribbling or incontinence should cease. In patients having radical prostatectomy for cancer, a successful operation will remove the tumor and prevent its spread to other areas of the body (**metastasis**). If examination of lymph nodes shows that cancer already had spread beyond the prostate at the time of surgery, other measures are available to control the tumor.

Technology

Responding to spoken instructions, a specially engineered robot has assisted in more than 500 operations to remove the prostate glands of cancer patients. Used by surgeons in the United States and Europe, the AESOP system is the first surgical robot approved by the Food and Drug Administration (FDA). By positioning a slender optical tube (endoscope) that is passed through the patient's body, the robotic arm allows the surgeon to view the minimally invasive surgery on a video monitor and use both hands to improve surgical precision and results while minimizing side effects. Patients spend about 12 hours in the hospital and return to work within two days.

Research

Early findings released by the Prostate Cancer Outcomes Study (PCOS) confirm that radical prostatectomy results in significant sexual dysfunction and some loss of urinary control. Initiated by the National Cancer Institute (NCI) in 1994, PCOS is the first systematic evaluation of how primary cancer treatments affect patients' quality of life.

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National Prostate Cancer Coalition. 1156 15th St., NW, Washington, DC 20005. (202) 463-9455. <www.4npcc.org>.

Prostate Health Council. American Foundation for Urologic Disease. 1128 N. Charles St., Baltimore, MD 21201-5559. (800) 828-7866. <http://www.afud.org>.

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Protein electrophoresis

Definition

Protein electrophoresis is a technique used to separate the different component proteins (fractions) in a mixture of proteins, such as a blood sample, on the basis of differences in how the components move through a fluid-filled matrix under the influence of an applied electric field.

Purpose

Protein electrophoresis is a **screening test** used to evaluate, diagnose, and monitor a variety of diseases and conditions through examination of the amounts and types of protein in a blood, urine, or cerebrospinal fluid (CSF) specimen.

Precautions

Certain other diagnostic tests or prescription medications can affect the protein electrophoresis results. The administration of a contrast dye used in some other tests may falsely elevate apparent protein levels. Drugs that can alter results include aspirin, bicarbonates, chlorpromazine (Thorazine), **corticosteroids**, isoniazid (INH), and neomycin (Mycifradin). The total serum protein concentration may also be affected by changes in the patient's posture or by the use of a tourniquet during the drawing of blood.

Because there is less protein in urine and CSF samples than in blood, these samples often must be concentrated before analysis. The added sample handling can lead to contamination and erroneous results. In collection of a CSF specimen, it is important that the sample not be contaminated with blood proteins that would invalidate the CSF protein measurements.

Description

Proteins—long chains of connected amino acids—are biologically important building-block chemicals that contain the elements carbon, hydrogen, nitrogen, and oxygen. Some proteins also contain sulfur, phosphorus, iron, iodine, selenium, or other trace elements. There are 22 amino acids commonly found in all proteins. The human body is capable of producing fourteen of these amino acids; the remaining eight are called essential amino acids, and must be obtained from food. Proteins are found in muscles, blood, skin, hair, nails, and the internal organs and tissues. Enzymes and antibodies are proteins, and many hormones are proteinlike. Electrophoresis is one of a variety of techniques that can be used to fractionate (separate) protein mixtures into individual component proteins.

The serum protein electrophoresis test requires a blood sample drawn by venipuncture (having blood drawn from a vein) performed in the doctor's office or on site at a medical laboratory. The urine protein electrophoresis test requires either an early morning urine sample or a 24-hour urine sample, according to the physician's request. A CSF specimen must be collected by **lumbar puncture** (spinal tap), generally performed by a physician as an outpatient procedure in a hospital. Because of risks associated with the lumbar-puncture procedure, the patient must sign a consent form, and should be prepared to remain for six to eight hours under observation.

Preparation

It is usually not necessary for the patient to restrict food or fluids before blood is drawn for a serum protein electrophoresis test; a four-hour fast is requested before drawing blood for lipoprotein testing. For protein electrophoresis on all types of samples, any factors that might affect test results, such as whether the patient is taking any medications, should be noted.

Aftercare

After a blood sample is drawn, a small bandage may be applied to the puncture site, and the patient may be cautioned about the possibility of fainting or of lightheadedness. Following lumbar puncture for the collection of CSF, the patient must be kept lying flat in the hospital under observation for at least six to eight hours.

Risks

Risks posed by the venipuncture are minimal but may include slight bleeding from the puncture site, the devel-

opment of a small bruise at the puncture site, or both. Other risks include fainting or lightheadedness after the sample is drawn. Lumbar puncture can lead to leakage of CSF from the puncture site, headache, infection, symptoms of meningitis, nausea, vomiting, or difficulty urinating. Rarely, pre-existing intracranial pressure can lead to brain herniation, resulting in brain damage or death.

Normal results

Blood proteins

Serum protein electrophoresis is used to determine the total serum protein concentration, which is an indication of the patient's hydration state: dehydration leads to high total serum protein concentration. Further, the levels of different blood proteins rise or fall in response to such disorders as cancer and associated protein-wasting syndromes, immune-system disorders, liver dysfunction, impaired nutrition, and chronic fluid-retaining conditions. The different types of blood proteins are separated into fractions of five distinct classes: albumin, alpha$_1$-globulins, alpha$_2$-globulins, beta-globulins, and gamma-globulins (immunoglobulins). In addition to standard protein electrophoresis, **immunoelectrophoresis** may be used to assess the blood levels of specific immunoglobulins. Immunoelectrophoresis is usually ordered when the serum protein electrophoresis test shows an unusually high amount of protein in the gamma-globulin fraction.

ALBUMIN Albumin, which is produced in the liver, is the most abundant blood protein. It makes a major contribution to the regulation of water movement between the tissues and the bloodstream. Albumin binds calcium, thyroid hormones, fatty acids, and many drugs, keeping them in the blood circulation and preventing them from being filtered out by the kidneys. Albumin levels can play a role in the effectiveness and toxicity of therapeutic drugs and in drug interactions.

GLOBULINS Serum globulins are separated in protein electrophoresis as four main fractions: alpha$_1$-, alpha$_2$-, beta-, and gamma-globulins.

- The major alpha$_1$-globulin is alpha$_1$-antitrypsin, produced by the lungs and liver. Alpha$_1$-antitrypsin deficiency is a marker of an inherited disorder characterized by an increased risk of emphysema.
- Alpha$_2$-globulins include serum haptoglobin, alpha$_2$-macroglobulin, and ceruloplasmin. Haptoglobin binds to hemoglobin, released from damaged red blood cells during hemolysis, to prevent its excretion by the kidneys. Alpha$_2$-macroglobulin accounts for about one third of the alpha$_2$-globulin fraction. Ceruloplasmin is involved in the storage and transport of copper and iron in the body.
- Beta-globulins include transferrin, low-density lipoproteins (LDL), and complement components. Transferrin transports dietary iron to the liver, spleen, and bone marrow. Low-density lipoprotein is the major carriers of cholesterol in the blood. Complement is a system of blood proteins involved in inflammatory response.
- The gamma-globulin fraction contains the immunoglobulins, a family of proteins that function as antibodies. Antibodies, in response to infection, allergic reactions, and organ transplants, recognize and bind foreign bodies, or antigens, to facilitate their destruction by the immune system. The **immune response** is regulated by a large number of antigen-specific gamma-globulins that fall into five main classes called IgG, IgA, IgM, IgB, and IgE. When the serum protein electrophoresis test demonstrates a significant deviation from the normal gamma-globulin levels, a supplemental test, immunoelectrophoresis, should be ordered to identify the specific globulin(s) involved.

The following serum protein electrophoresis reference values are representative; some variation among laboratories and specific methods is to be expected. (1 gm = approximately 0.02 pt and 1 dl = approximately 0.33 fluid oz.)

- Total protein: 6.4–8.3 g/dL
- Albumin: 3.5–5.0 g/dL
- Alpha$_1$-globulin: 0.1–0.3 g/dL
- Alpha$_2$ globulin: 0.6–1.0 g/dL
- Beta-globulin: 0.7–1.2 g/dL
- Gamma-globulin: 0.7–1.6 g/dL

Urinary proteins

Protein electrophoresis is performed on urine samples to classify disorders that cause protein loss via the kidneys. In urine, normally no globulins and less than 0.050 g/dL albumin are present.

Cerebrospinal fluid (CSF) proteins

In CSF, the total protein concentration is normally 0.015–0.045 g/dL, with gamma-globulin accounting for 3% to 12%. The main use of CSF protein electrophoresis testing is in the diagnosis of central nervous tumors and multiple sclerosis.

Abnormal results

Deviations in serum protein levels from reference levels are considered in conjunction with symptoms and results from other diagnostic procedures.

KEY TERMS

Acute-phase proteins—Proteins produced during the acute-phase response, a set of physiological changes that occur in response to biologic stress such as trauma or sepsis.

Albumin—A blood protein produced in the liver that helps to regulate water distribution in the body.

Antibodies—Immunoglobulin protein molecules produced by B cells during the immune response. Each antibody recognizes an individual antigen to trigger immune defenses.

Antigen—Foreign body that triggers immune response.

Bence-Jones protein—The Ig light chain, part of an immunoglobulin, that is detected by urine protein electrophoresis in the case of multiple myeloma.

Complement—A group of complex proteins of the beta-globulin type in the blood that bind to antibodies during anaphylaxis. In the complement cascade, each complement interacts with another in a pattern that causes fluid build-up in cells, leading to lysis (cell destruction).

Electrophoresis—A technique used to separate the proteins in a biological sample on the basis of differences in how the components move through a fluid-filled matrix under the influence of an applied electric field.

Globulins—A group of proteins in blood plasma whose levels can be measured by electrophoresis in order to diagnose or monitor a variety of serious illnesses.

Hemolysis—Also called hematolysis, the breakage of red blood cells and concomitant liberation of hemoglobin.

Lumbar puncture—Also called spinal tap, a procedure for the withdrawal of spinal fluid from the lumbar region of the spinal cord for diagnosis, or for injection of a dye for imaging, or for administering medication or an anesthetic.

Paraprotein—A paraprotein is an immunoglobulin produced by a clone of identical B cells.

Protein—Proteins, such as enzymes and antibodies, are biologically important molecules made of long chains of connected amino acids that contain the elements carbon, hydrogen, nitrogen, and oxygen. Certain proteins may also contain sulfur, phosphorus, iron, iodine, selenium, or other trace elements.

Albumin levels are increased in dehydration and decreased in malnutrition, pregnancy, liver disease, inflammatory diseases, and protein-losing states such as malabsorption syndrome and certain kidney disorders. Low serum albumin levels can indicate disease and can influence analysis of thyroid hormones and calcium.

Alpha$_1$-globulins are increased in inflammatory diseases and decreased or absent in juvenile pulmonary emphysema, a hereditary disease.

Alpha$_2$-globulins are increased in acute and chronic inflammation and nephrotic syndrome. Decreased values may indicate hemolysis (the release of hemoglobin from red blood cells). Low haptoglobin can indicate tumor **metastasis**, severe sepsis, or chronic liver disease. The concentration of macroglobulin is increased during nephrosis. Ceruloplasmin concentration is increased during pregnancy and decreased in Wilson's disease, a rare inherited condition that leads to accumulation of copper in the liver.

Beta-globulin levels are increased in **multiple myeloma** and also in conditions of high cholesterol (hypercholesterolemia), such as in atherosclerosis, and in iron deficiency **anemia**. Levels are decreased in coagulation disorders.

Gamma-globulin levels are increased in multiple myeloma. The levels are increased as well in chronic inflammatory disease and autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus, cirrhosis, and acute and chronic infection. The gamma-globulins are decreased in leukemia, in a variety of genetic immune disorders, and in secondary immune deficiency related to steroid use or to severe infection. Immunoglobulin deficiency due to inherited disorders can range from partial or complete loss of a single immunoglobulin class to complete absence of all immunoglobulins.

Finding an individual (oligoclonal) band in the gamma fraction of the electrophoresis result indicates the presence of a paraprotein. Type IgG or IgA paraproteins associated with multiple myeloma may be found by serum protein electrophoresis testing; however, the tumor may also produce only Ig light chains that are removed from the blood by the kidneys. This Ig light chain (also known as the Bence-Jones protein) is

detected by urine protein electrophoresis and is found nearly exclusively in patients with multiple myeloma.

In urine samples, abnormal results other than the presence of the Bence-Jones protein indicate disruption of kidney function or acute inflammation. Hemoglobin and myoglobin are found in the urine of patients with infection or hemolysis.

An increase in total protein concentration in the CSF is often found with central nervous system (CNS) tumors and in meningitis.

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Proteomics

Definition

Proteomics is the systematic study of all of the proteins in a cell, tissue, or organism.

Description

The term proteome was coined in 1994 to describe all of the proteins in a given cell, tissue, or organism. Proteomes are extremely complex and differ among individuals, cell types, and within the same cell depending on cell activity, stimuli, and disease. There are estimated to be between one and ten million different proteins in the human body. Relatively few of these proteins have been identified.

Proteomics is being developed for use in cancer diagnosis and treatment. A protein pattern or array from blood or a cancer cell eventually may be the primary means of diagnosing cancer. Although significant advances have been made in clinical studies, as of 2005, proteomics was not yet available in clinical settings.

Proteomics technology for cancer diagnosis and treatment identifies biomarkers—proteins and protein patterns in blood, urine, and tissue that can be used to detect:

- early cancers
- treatment response
- the likelihood of relapse after treatment

It is expected that proteomics will be used to:

- develop better cancer treatments
- predict the effects of various treatments
- develop individualized therapies for each patient

Proteomics has led to the identification of many biomarker proteins and the discovery of many new proteins in the blood. As of 2005, proteomics has been used to identify hundreds of proteins in the ovary, prostate, breast, and esophagus that increase or decrease as cells begin to grow abnormally.

Procedures

Progress in proteomics has been made possible by the development of new technologies including:

- high-resolution mass spectrometry (MS) that can sort out thousands of proteins and protein fragments on the basis of their molecular weight and electrical charge
- sophisticated artificial intelligence computer programs that can learn to identify the specific patterns of a few proteins present in a huge protein array
- laser capture microdissection microscopes that use low-energy laser beams and special transfer film to lift single cells from a tissue, to collect and analyze all of the proteins in the cell by (MS) and computer technology

A mass spectrometer consists of:

- an ionization source that removes electrons from (ionizes) the proteins and protein fragments in a sample so that they all have a positive charge
- a mass analyzer that measures the mass-to-charge ratio (m/z) of the ionized (charged) proteins and fragments, as gases under a vacuum
- a detector that determines the number of ions present at each m/z value

The result is a mass spectrum or chart with a series of spikes or peaks, each representing a charged protein fragment from the sample. The height of each peak represents the amount of that particular protein or fragment that is present in the sample. The size of the peaks and the distance between them is the protein pattern or array of the entire sample. Each spectrum may have more than 15,000 data points—one for every protein and protein fragment—with their molecular weight and intensity values reflecting their relative abundance in the sample.

Computers rapidly analyze the MS data searching for subtle differences among multiple protein patterns and for proteins that might serve as biomarkers. Once potential biomarkers are identified, the computer is trained to sort through the patterns of thousands of proteins for the few small protein biomarkers that can distinguish between cancer and control samples or between cancer protein patterns before and after treatment.

MS-based proteomic analysis is very fast. The entire process—from collecting a few drops of blood to the spectral analysis—can occur in less than one minute. Extremely small amounts of protein can be detected and hundreds of samples can be analyzed sequentially.

Laser capture microdissection microscopes enable scientists to use tissue removed from a patient by a **biopsy** to isolate pure samples of normal cells, precancerous cells, and tumor cells from a single tissue of a single patient. Analysis of the protein patterns from these cells enable researchers to study:

- patterns that may predict early-stage cancer
- how a particular treatment affects the network of proteins in a cell
- early signs of cancer drug toxicity
- mechanisms of drug resistance
- means for reducing side effects of treatment
- changes in protein patterns during tumor recurrenceIt may be possible to predict from the protein patterns which patients are likely to have an early toxic response to a treatment, so that doses can be lowered or a different treatment can be chosen.

Initially, researchers are concentrating on ovarian and prostate cancers, which usually are not detected in early stages when the cancer is progressing without symptoms. By using proteomics for early detection, tumors may be treated before they spread (metastasize) to other parts of the body. Scientists also are studying the most common, solid human tumors including breast, colon, lung, and pancreatic cancers.

Cancers

Ovarian cancer

More than 80% of ovarian cancers are not diagnosed until they have reached an advanced stage when the five-year-survival rate is 20% or less. However in the 20% of women whose **ovarian cancer** is diagnosed at an early stage, the prognosis is excellent, with a five-year-survival rate of over 95%.

In 2002 researchers used MS-based proteomics to examine the protein patterns in blood serum, obtained with a finger prick, from 50 patients with stage-I ovarian cancer and 66 controls who were either healthy or had a benign (non-cancerous) condition such as ovarian cysts, fibroids, endometriosis, or general inflammatory disease. Such conditions are much more common than ovarian cancer but may have symptoms that suggest the possibility of cancer. Out of the complex patterns of tens of thousands of serum proteins, the computer identified a specific combination of five proteins that could distinguish between the cancer patients and the controls. Using this identified sub-pattern, all of the cancer patients tested positive—a 100% sensitivity. Among the controls, 5% were false positives demonstrating a specificity of 95%.

In 2004, using higher-resolution MS, a different protein pattern, and a larger group of patients and controls, researchers were able to achieve 100% sensitivity and specificity for diagnosing ovarian cancer. However validation of the procedure on a large clinical sample is needed before a commercial test becomes available. These clinical studies are being carried out in high-risk clinics, in which many women are considering prophylactic oophorectomies—removal of the ovaries—to prevent ovarian cancer, because they have a family history of the disease or carry mutations in the BRCA genes that greatly increase their risk for breast and ovarian cancers.

As of 2005, a clinical trial also was underway comparing proteomics with standard CA-125 blood tests that use a single protein as a biomarker for ovarian cancer. The blood protein CA-125 may be elevated in women with benign conditions as well as ovarian cancer. Another ongoing clinical trial is attempting to use proteomics to predict the early recurrence of ovarian cancer.

The small low-level proteins that have proven useful for the proteomics of ovarian cancer have been found to accumulate on large carrier blood proteins such as albumin. Scientists have found that by extracting the carrier-protein fraction of the blood they can obtain much higher quantities of these biomarkers.

Prostate cancer

Prostate specific antigen (PSA) levels are used as a preliminary screen for **prostate cancer**. However 70–75% of men who undergo biopsies because of abnormal PSA levels do not have cancer. It has been difficult to rule-out cancer without a biopsy in patients with slightly elevated PSA levels (4–10 nanograms per ml). MS-based proteomics of the blood proteins in 167 patients with prostate cancer, 77 patients with benign prostate hyperplasia, and 82 healthy males correctly classified 96% of the samples as either prostate cancer or non-cancer including benign prostate hyperplasia. Most of the

cancers were correctly identified and the specificity was 71%, meaning that were a number of false positives. The test was effective in men with normal, slightly elevated, and high PSA levels. Thus proteomics may prove useful for choosing whether to perform a biopsy and may reduce the incidence of unnecessary biopsies.

Molecules called phosphates commonly are added to or removed from proteins to change their activity or function. Specific changes in phosphorylated proteins—those with attached phosphates—are believed to be important for prostate cancer progression. Researchers are studying whether changes in phosphorylation, as detected by MS-based proteomics, can be used as biomarkers for diagnosing the progression of prostate and other cancers.

Breast cancer

Proteomic studies on **breast cancer** have found a combination of three blood proteins that may be useful for discriminating between women with breast cancer, women with benign breast disease, and healthy women. About 70–80% of breast cancers originate in the mammary ducts—the thin tubes that lead to the nipples. Nipple aspirate fluid from these ducts has a higher concentration of breast-specific proteins than blood. Possible tumor-marker proteins from this fluid are being studied by proteomics.

A 2003 proteomics study successfully identified fluctuating levels of specific active proteins inside breast and ovarian tumor cells. This may help determine early in treatment whether a particular drug is effective in a given patient.

About 25–30% of women with breast cancer have high levels of the protein Her-2/neu on the surfaces of their cancer cells. The cancer drug **Herceptin** is an antibody that attaches to Her-2/neu and prevents the protein from promoting cancer cell growth. Ongoing proteomics studies are monitoring key signaling systems in cells that may be influenced by Herceptin and other cancer drugs that target specific molecules. Proteomics has been used to measure the levels of active and inactive signaling proteins in isolated cancer cells obtained from tumor biopsies before and at various times after drug treatment. It has been found that breast cancer patients with a poor prognosis have more of the active form of the protein AKT that promotes cell survival. Herceptin lowers this AKT levels, promoting tumor cell death.

Other cancers

A 2004 proteomics study found a protein pattern that may predict which people with familial adenomatous polyposis (FAP)—an inherited condition that often leads to colon cancer—will respond to the preventive drug celecoxib. Protein patterns from patients before and after drug treatment distinguished between those in which celecoxib decreased the number of colon polyps that are characteristic of FAB and those who did not respond to the drug. One particular protein peak appeared only in patterns from non-responsive patients. A few protein peaks changed significantly in all patients following treatment with celecoxib.

Scientists are searching for blood protein patterns that may predict a person's risk for prostate cancer, pancreatic cancer, and **melanoma**. Protein patterns have been found in tumor tissue from lung and bladder cancers that may be able to discriminate between cancerous and healthy tissues.

As of 2005 proteomics **clinical trials** were testing blood protein patterns to:

- determine the response to **radiation therapy** in patients with localized prostate cancer and identify patients who might benefit from aggressive treatment
- predict the development of **non-small cell lung cancer** in patients with suspicious lung abnormalities
- determine whether a patient has a type of **lymphoma** known as mycosis fungoides/cutaneous T-cell lymphoma

KEY TERMS

Biomarker—A distinctive biological indicator of a condition or process.

Biopsy—The removal of a small piece of tissue for examination.

Laser capture microdissection microscope—An instrument that uses low-energy laser beams and special transfer film to lift single cells from a tissue.

Mass spectroscopy, MS—A technique that separates mixtures of substances on the basis of molecular weight and electrical charge.

Mass-to-charge ratio, m/z—The ratio of the molecular mass of a substance to its electrical charge; used for protein separation by MS.

Phosphorylation—The enzymatic addition of a phosphate group to a protein.

Prostate specific antigen, PSA—A biomarker used as a preliminary screen for prostate cancer.

Protein array—The pattern of proteins in blood, tissue, or a cell as determined by MS.

Proteome—The collection of all of the proteins in a cell, tissue, or organism.

• predict whether patients with psoriasis or **cutaneous T-cell lymphoma** will remain in remission.

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Margaret Alic, Ph.D.

Pruritis *see* **Itching**

Psycho-oncology

Definition

Psycho-oncology is a broad-based approach to cancer therapy that treats the emotional, social, and spiritual distress which often accompanies cancer. According to Dr. Jimmie Holland, the founder of psycho-oncology, the field has two major emphases. The first is the study of cancer patients' psychological reactions to their illness at all stages of its course; the second is analysis of the emotional, spiritual, social, and behavioral factors that influence the risk of developing cancer and long-term survival following treatment. Some psycho-oncologists consider their field a subspecialty of psychiatry while others emphasize its multidisciplinary aspects. In addition to psychiatrists, departments of psycho-oncology in major cancer centers may include nurses, surgeons, bioethicists, social workers, psychologists, clergy, palliative care specialists, and volunteers.

Description

Psycho-oncology is a relatively new addition to the care of cancer patients. It began in the mid-1970s when Dr. Holland returned to the practice of psychiatry after her children were in school. Married to an oncologist,

she had noted that her husband's colleagues focused on the physical effects of the anticancer drugs they were giving their patients to the point of failing to take the patients' thoughts and emotions into account. To some extent this oversight was part of the medical culture of the 1950s and 1960s; at that time cancer carried a stigma because it had low rates of survival. Many doctors were taught in medical school to withhold a diagnosis of cancer from the patient on the grounds that the disease was virtually a death sentence and the truth would be unbearable. Such highly regarded newspapers as the *New York Times* even refused to print the words "breast cancer" when the founders of the Reach to Recovery program first wanted to insert notices of their meetings.

In the 1970s, however, this attitude of shame and secrecy was reversed, partly because of the patients' rights movement, but also because newer and more effective treatments for cancer came into use and the number of long-term survivors of cancer increased. In 1977 Dr. Holland started the first full-time psychiatric service in a cancer research center in order to study and treat the emotional and psychological crises experienced by cancer patients. She conducted some of the earliest research studies of the emotional impact of cancer on patients and their families.

In the early 2000s, psycho-oncology has become an accepted part of cancer treatment, with departments of psycho-oncology established in most major cancer centers in Canada and the United States. The field has its own journal, *Psycho-Oncology*, as well as national and international societies for interested professionals.

Special concerns

Special concerns in psycho-oncology include the feelings of guilt or anxiety expressed by many cancer patients that they cannot adopt or maintain the positive attitudes that some people believe are essential to fighting cancer. Such patients feel burdened by the notion—sometimes voiced by family members—that their literal survival depends on visualizations (usually visualizations of their immune system combating the cancer) or otherwise acting cheerful and upbeat. In addition, some extreme forms of New Age thought lead some people to "blame the victim" that is, to say such things to cancer patients as, "You must have subconsciously wanted to develop this cancer," or, "It's your bad karma—you must have done something bad in a previous existence to deserve this disease." Psycho-oncologists, however, do not regard mental attitudes toward cancer as the sole factor affecting long-term survival, and they do not insist that patients adopt a one-size-fits-all approach to coping with cancer. Dr. Holland's list of recommendations for coping with cancer emphasizes flexibility, as she urges patients to:

- Use coping techniques or patterns that have helped them in the past in dealing with the stresses of life. For example, someone who has been helped by talking through their problems with trusted friends or family members should not suddenly start to keep their problems to themselves in coping with cancer.
- Take the "one-day-at-a-time" approach in dealing with the symptoms and other problems that cancer brings with it. This approach, which is sometimes called "chunking it down," helps by keeping large-scale worries about the long-term future manageable.
- Seek out a doctor with whom they feel comfortable. A doctor/patient relationship based on trust and mutual respect makes it easier to ask appropriate questions and to be a full participant in treatment planning.
- Continue to draw on religious or spiritual beliefs and practices that have been helpful in the past. Patients who do not consider themselves religious or spiritual may still find comfort in activities that they found meaningful or inspiring, such as the performing arts or nature walks.
- Keep a notebook for recording dates of treatments, medication side effects, laboratory test results, x-ray findings, etc. This record can be valuable in monitoring or evaluating one's emotional ups and downs as well as changes in physical health.
- Keep a journal or diary for expressing feelings and emotional reactions. This record also may be useful in providing perspective.

Psycho-oncologists may also help patients deal with the increasing complexity of cancer therapy, as many patients have treatment teams consisting of several physicians in different subspecialties as well as social workers, nurses, clergy, and other professionals. Some patients experience the sheer number of caregivers involved in their treatment as an additional source of stress.

Treatments

Psycho-oncologists emphasize the importance of treating cancer patients as individuals with unique patterns of emotional responses to the disease as well as unique physical responses to medical and surgical treatments. Consequently, psycho-oncologists tailor their treatment to the needs and concerns of each patient. As of the early 2000s, psycho-oncologists may provide one or more of the following treatments for or services to cancer patients:

KEY TERMS

Bioethics—A field of study concerned with the moral and spiritual implications of medical research and treatments.

Distress—In general, any acute feeling of pain, anxiety, or sadness; in the context of psycho-oncology, any unpleasant emotion that interferes with a cancer patient's ability to cope with symptoms and treatment.

New Age thought—A general term for a set of beliefs that became popular in the 1970s but had been previously associated with the occult, secret doctrines and teachings, or paranormal phenomena. New Age writers commonly believe that the mind can control the body; some believe that this control includes disease processes.

Oncology—The medical specialty that deals with the development, diagnosis, and treatment of cancer.

Visualization—A technique for forming mental images or pictures of the healing process as a way of strengthening the immune system and/or fighting such disease agents as cancer cells or the AIDS virus.

QUESTIONS TO ASK YOUR DOCTOR

- How do you feel about my use of complementary or alternative therapies as part of my treatment program? Are there any that you would advise against?
- What reading materials or other resources would you recommend so that I can help myself cope with my symptoms and the side effects of cancer treatment?
- Where do you fit my emotional, psychological, and spiritual concerns into my treatment regimen?

- individual psychotherapy or counseling
- leading support groups for patients and family members
- crisis intervention
- medication management
- strategies for dealing with pain and other physical symptoms of cancer
- monitoring the patient's emotional distress level
- referrals to a pastoral counselor in the patient's faith tradition

Many psycho-oncologists use a pain scale, "distress thermometer," or self-administered questionnaires as a way of identifying the patient's specific areas of concern as well as monitoring his or her levels of distress at various points in the treatment process. Some commonly used questionnaires are the Mental Adjustment to Cancer (MAC) scale, first published in the United Kingdom in 1987; the Brief Symptom Inventory (BSI); and the Distress Management Screening Measure (DMSM), a newer scale that was tested in the United States in 2003–2004. Sample questions from these self-administered measures, as well as explanations of the treatments offered to cancer patients at different levels of emotional distress, can be found in *Distress*, a 32-page booklet available free of charge from the American Cancer Society and the National Comprehensive Cancer Network (NCCN).

Psycho-oncologists may also provide specialized counseling in the areas of death and bereavement or sex therapy if they have the appropriate training, or they may refer patients with these needs to qualified counselors in those fields.

Alternative and complementary therapies

Most psycho-oncologists support patients' use of complementary and alternative (CAM) therapies provided that they do not interfere with the patient's surgery, **chemotherapy**, or other mainstream treatments. Dr. Larry Dossey, a well-known expert in the field of alternative medicine, thinks that cancer patients are drawn to CAM treatments because they address questions about the larger meaning of illness that many patients have. He says, "The immense popularity of alternative therapies . . . may be due in large measure to the fact that they help people find meaning in their lives when they need it most." Significantly, several studies of cancer patients who have integrated CAM approaches into their treatment regimens have *not* found that these patients are more distressed or more likely to develop psychiatric disorders than patients who rely on conventional treatments alone.

As of 2005, the National Cancer Institute (NCI) and the National Center for Complementary and Alternative Medicine (NCCAM) are jointly funding **clinical trials** of several complementary and alternative treatments for cancer. Present trials include studies of yoga, Reiki, acupuncture, massage therapy (for cancer-related **fatigue**),

hyperbaric oxygen therapy, **mistletoe** extract, and pancreatic enzyme therapy (for pancreatic cancer). Details of these clinical trials are available on the NCCAM website.

New trends in research in psycho-oncology

Areas of particular concern to psycho-oncologists in the early 2000s include cultural differences that affect people's patterns of coping with cancer, and the long-term psychological effects of being a cancer survivor. With regard to the first, recent European studies suggest that English-speaking patients and patients from southern Europe have different styles of coping with cancer diagnosis and treatment even though both groups have similar percentages of highly distressed patients. With regard to survivorship, the Behavioral Research Center of the American Cancer Society is conducting a long-term study of cancer survivors' quality of life, with a special focus on their psychological adjustment and family relationships, to be completed in 2015.

See also Depression; Posttraumatic stress disorder.

Resources

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ORGANIZATIONS

American Psychosocial Oncology Society (APOS). 2365 Hunters Way, Charlottesville, VA 22911. (434) 293-5350. <http://www.apos-society.org>.

Behavioral Research Center, American Cancer Society. 1599 Clifton Road NE, Atlanta, GA 30329. (800) 758-0227 or (404) 329-7772. <http://www.cancer.org>.

National Comprehensive Cancer Network (NCCN). 500 Old York Road, Suite 250, Jenkintown, PA 19046. (215) 690-0300. <http://www.nccn.org>. The NCCN is a consortium of 19 major cancer centers in the United States.

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Rebecca Frey, PhD

R

Radiation therapy

Definition

Radiation therapy, sometimes called radiotherapy, x-ray therapy radiation treatment, cobalt therapy, electron beam therapy, or irradiation uses high energy, penetrating waves or particles such as x rays, gamma rays, proton rays, or neutron rays to destroy cancer cells or keep them from reproducing.

Purpose

The purpose of radiation therapy is to kill or damage cancer cells. Radiation therapy is a common form of cancer therapy. It is used in more than half of all cancer cases. Radiation therapy can be used:

- alone to kill cancer
- before surgery to shrink a tumor and make it easier to remove
- during surgery to kill cancer cells that may remain in surrounding tissue after the surgery (called intraoperative radiation)
- after surgery to kill cancer cells remaining in the body
- to shrink an inoperable tumor in order to reduce pain and improve quality of life
- in combination with **chemotherapy**

For some kinds of cancers such as early-stage **Hodgkin's disease**, **non-Hodgkin's lymphomas**, and certain types of prostate or brain cancer, radiation therapy alone may cure the disease. In other cases, radiation therapy used in conjunction with surgery, chemotherapy, or both, increases survival rates over any of these therapies used alone.

Precautions

Radiation therapy does not make the person having the treatments radioactive. In almost all cases, the benefits of this therapy outweigh the risks. However radiation therapy can have has serious consequences, so anyone contemplating it should be sure to understand why the treatment team believes it is the best possible treatment option for their cancer. Radiation therapy is often not appropriate for pregnant women, because the radiation can damage the cells of the developing baby. Women who think they might be pregnant should discuss this with their doctor.

Description

Radiation therapy is a local treatment. It is painless. The radiation only acts on the part of the body that is exposed to the radiation. This is very different from chemotherapy in which drugs circulate throughout the whole body. There are two main types of radiation therapy. In external radiation therapy a beam of radiation is directed from outside the body at the cancer. In internal radiation therapy, called brachytherapy or implant therapy, a source of radioactivity is surgically placed inside the body near the cancer.

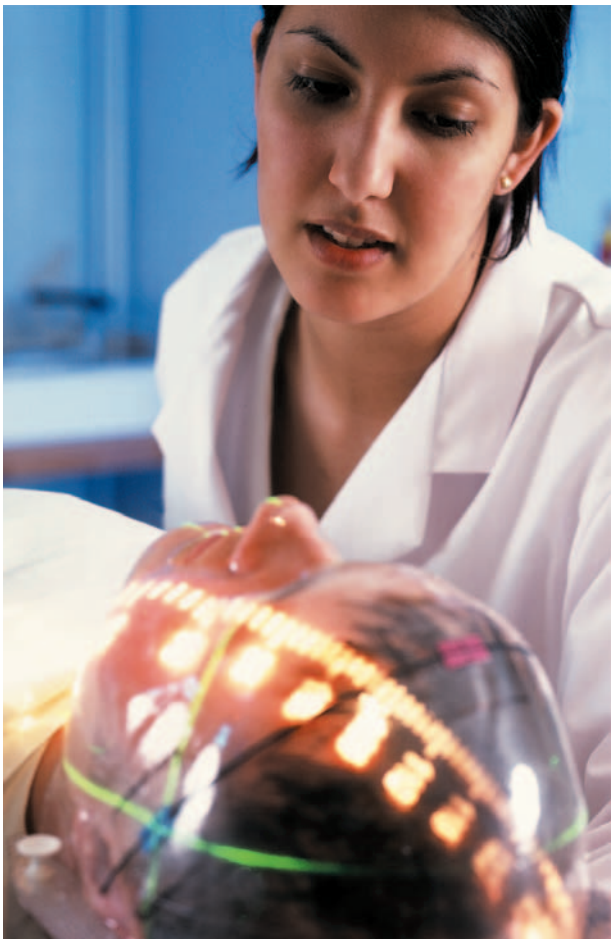
How radiation therapy works

The protein that carries the code controlling most activities in the cell is called deoxyribonucleic acid or DNA. When a cell divides, its DNA must also double and divide. High-energy radiation kills cells by damaging their DNA. This blocks their ability to grow and increase in number.

One of the characteristics of cancer cells is that they grow and divide faster than normal cells. This makes them particularly vulnerable to radiation. Radiation also damages normal cells, but because normal cells are growing more slowly, they are better able to repair radiation damage than are cancer cells. In order to give normal cells time to heal and reduce side effects, radiation treatments are often given in small doses over a six- or seven-week period.

External radiation therapy

External radiation therapy is the most common kind of radiation therapy. It is usually done during outpatient



Radiographer prepares a patient for radiation therapy. She is aiming laser cross-hairs onto the site of a brain tumor. The patient's head is protected and held in place by a plastic mask. *(Copyright Simon Fraser, Science Source/Photo Researchers, Inc. Photo reproduced by permission.)*

visits to a hospital clinic and is usually covered by insurance.

Once a doctor called a radiation oncologist determines the proper dose of radiation for a particular cancer, the dose is divided into smaller doses called fractions. One fraction is usually given each day, five days a week for six to seven weeks. However, each radiation plan is individualized depending on the type and location of the cancer and what other treatments are also being used. The actual administration of the therapy usually takes about half an hour daily, although radiation is only administered for one to five minutes at each session. It is important to attend every scheduled treatment to get the most benefit from radiation therapy.

Recently, trials have begun to determine if there are ways to deliver radiation fractions so that they kill more cancer cells or have fewer side effects. Some trials use smaller doses given more often. Up-to-date information on voluntary participation in **clinical trials** and where they are being held is available by entering the search term "radiation therapy" at the following web sites:

- National Cancer Institute. <http://cancer-trials.nci.nih.gov> or (800) 4-CANCER.
- National Institutes of Health Clinical Trials. <http://clinicaltrials.gov>
- Center Watch: A Clinical Trials Listing. <http://www.centerwatch.com>.

The type of machines used to administer external radiation therapy and the material that provides the radiation vary depending on the type and location of the cancer. Generally, the patient puts on a hospital gown and lies down or sits in a special chair. Parts of the body not receiving radiation are covered with special shields that block the rays. A technician then directs a beam of radiation to a pre-determined spot on the body where the cancer is located. The patient must stay still during the administration of the radiation so that no other parts of the body are affected. As an extra precaution in some treatments, special molds are made to make sure the body is in the same position for each treatment. However, the treatment itself is painless, like having a bone x-rayed.

Internal radiation therapy

Internal radiation therapy is called brachytherapy, implant therapy, interstitial radiation, or intracavitary radiation. With internal radiation therapy, a bit of radioactive material is sealed in an implant (sometimes called a seed or capsule). The implant is then placed very close to the cancer. The advantage of internal radiation therapy is that it concentrates the radiation near the cancer and lessens the chance of damage to normal cells. Many different types of radioactive materials can be used in the implant, including cesium, iridium, iodine, phosphorus, and palladium.

How the implant is put near the cancer depends on the size and location of the cancer. Internal radiation therapy is used for some cancers of the head, neck, thyroid, breast, female reproductive system, and prostate. Most people will have the radioactive capsule implanted by a surgeon while under either general or local anesthesia at a hospital or surgical clinic.

Patients receiving internal radiation therapy do become temporarily radioactive. They must remain in the hospital during the time that the implant stays in place. The length of time is determined by the type of cancer and the dose of radioactivity to be delivered. During the time the implant is in place, the patient will have to stay in bed and remain reasonably still.

While the implant is in place, the patient's contact with other people will be limited. Health care workers will make their visits as brief as possible to avoid exposure to radiation, and visitors, especially children and pregnant women, will be limited.

The implant usually can be removed in a simple procedure without an anesthetic. As soon as the implant is out of the body, the patient is no longer radioactive, and restrictions on being with other people are lifted. Generally people can return to a level of activity that feels comfortable to them as soon as the implant is removed. Occasionally the site of the implant is sore for some time afterwards. This discomfort may limit specific activities.

In some cases, an implant is left permanently inside the body. People who have permanent implants need to stay in the hospital and away from other people for the first few days. Gradually the radioactivity of the implant decreases, and it is safe to be around other people.

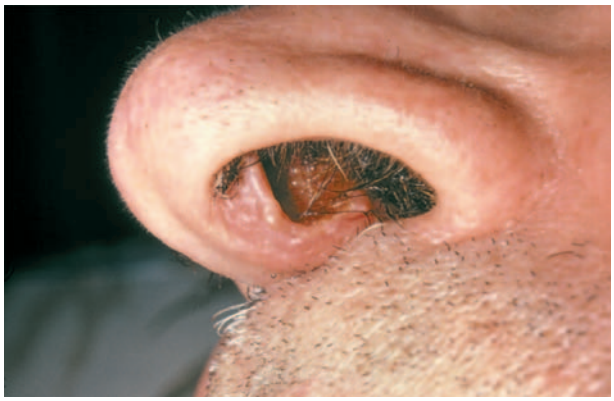
Radioimmunotherapy

Radioimmunotherapy is a promising way to treat cancer that has spread (metastasized) to multiple locations throughout the body. Antibodies are immune system proteins that specifically recognize and bind to only one type of cell. They can be designed to bind only with a certain type of cancer cell. To carry out radioimmunotherapy, antibodies with the ability to bind specifically to a patient's cancer cells are attached to radioactive material and injected into the patient's bloodstream. When these man-made antibodies find a cancer cell, they bind to it. Then the radiation kills the cancer cell. This process is still experimental, but because it can be used to selectively attack only cancer cells, it holds promise for eliminating cancers that have spread beyond the primary tumor.

Radiation used to treat cancer

PHOTON RADIATION Early radiation therapy used x rays like those used to take pictures of bones, or gamma rays. X rays and gamma rays are high-energy rays composed of massless particles of energy (like light) called photons. The distinction between the two is that gamma rays originate from the decay of radioactive substances (like radium and cobalt-60), while x rays are generated by devices that excite electrons (such as cathode ray tubes and linear accelerators). These high-energy rays act on cells by disrupting the electrons of atoms within the molecules inside cells, disrupting cell functions, and, most importantly, by stopping their ability to divide and make new cells.

PARTICLE RADIATION Particle radiation is radiation delivered by particles that have mass. Proton therapy has been used since the early 1990s. Proton rays consist of protons, a type of positively charged atomic particle, rather than photons, which have neither mass nor charge. Like x rays and gamma rays, proton rays disrupt cellular activity. The advantage of using proton rays is that they can be shaped to conform to the irregular shape of the tumor more precisely than x rays and gamma rays. They allow delivery of higher radiation doses to tumors without increasing damage to the surrounding tissue.



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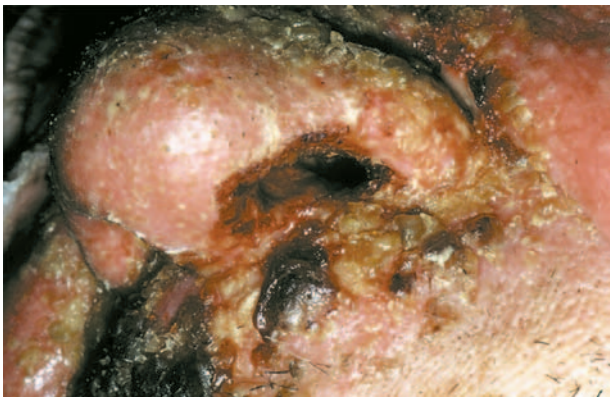
Neutron therapy is another type of particle radiation. Neutron rays are very high-energy rays. They are composed of neutrons, which are particles with mass but no charge. The type of damage they cause to cells is much less likely to be repaired than that caused by x rays, gamma rays, or proton rays.

Neutron therapy can treat larger tumors than conventional radiation therapy. Conventional radiation therapy depends on the presence of oxygen to work. The center of large tumors lack sufficient oxygen to be susceptible to damage from conventional radiation. Neutron radiation works in the absence of oxygen, making it especially effective for the treatment of inoperable **salivary gland tumors**, bone cancers, and some kinds of advanced cancers of the pancreas, bladder, lung, prostate, and uterus.

Recent advances in radiation therapy

A newer mode of treating brain cancers with radiation therapy is known as stereotactic radiosurgery. As of the early 2000s, this approach is limited to treating cancers of the head and neck because only these parts of the body can be held completely still throughout the procedure. Stereotactic radiosurgery allows the doctor to deliver a single high-level dose of precisely directed radiation to the tumor without damaging nearby healthy brain tissue. The treatment is planned with the help of



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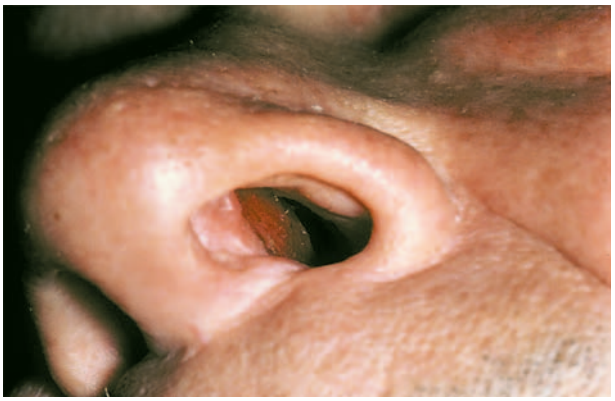

Before, two weeks after, and six months after radiation therapy to treat squamous cell carcinoma inside the left nostril. *(Copyright Dr. P. Marazzi, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

three-dimensional computer-aided analysis of CT and MRI scans. The patient's head and neck are held steady in a skeletal fixation device during the actual treatment. Stereotactic radiosurgery can be used in addition to standard surgery to treat a recurrent brain tumor, or in place of surgery if the tumor cannot be reached by standard surgical techniques.

Two major forms of stereotactic radiosurgery are in use as of 2003. The gamma knife is a stationary machine that is most useful for small tumors, blood vessels, or similar targets. Because it does not move, it can deliver a small, highly localized and precise beam of radiation. Gamma knife treatment is done all at once in a single hospital stay. The second type of radiosurgery uses a movable linear accelerator-based machine that is preferred for larger tumors. This treatment is delivered in several small doses given over several weeks. Radiosurgery that is performed with divided doses is known as fractionated radiosurgery. The total dose of radiation is higher with a linear accelerator-based machine than with gamma knife treatment.

Another advance in intraoperative radiotherapy (IORT) is the introduction of mobile devices that allow the surgeon to use radiotherapy in early-stage disease and to operate in locations where it would be difficult to transport the patient during surgery for radiation treatment. Mobile IORT units have been used successfully as of 2003 in treating early-stage breast cancer and rectal cancer.

Radiation sensitizers are another recent innovation in radiation therapy. Sensitizers are medications that are given to make cancer cells easier to kill by radiation than normal calls. Gemcitabine (Gemzar) is one of the drugs most commonly used for this purpose.

Preparation

Before radiation therapy, the size and location of the patient's tumor are determined very precisely using **magnetic resonance imaging** (MRI) and/or **computed tomography** scans (CT scans). The correct radiation dose, the number of sessions, the interval between sessions, and the method of application are calculated by a radiation oncologist based on the tumor type, its size, and the sensitivity of the nearby tissues.

The patient's skin is marked with a semi-permanent ink to help the radiation technologist achieve correct positioning for each treatment. Molds may be built to hold tissues in exactly the right place each time.

Aftercare

Many patients experience skin burn, **fatigue**, nausea, and vomiting after radiation therapy regardless of where the radiation is applied. After treatment, the skin around the site of the treatment may also become sore. Affected skin should be kept clean and can be treated like sunburn, with skin lotion or vitamin A and D ointment. Patients should avoid perfume and scented skin products and protect affected areas from the sun.

Nausea and vomiting are most likely to occur when the radiation dose is high or if the abdomen or another part of the digestive tract is irradiated. Sometimes nausea and vomiting occur after radiation to other regions, but in these cases the symptoms usually disappear within a few hours after treatment. Nausea and vomiting can be treated with antacids, Compazine, Tigan, or Zofran.

KEY TERMS

Anemia—Insufficient red blood cells in the body.

Antibody—Protein molecule that recognizes and binds specifically to a foreign substance in the body in order to eliminate it.

Chemotherapy—Injecting drugs into the body where they circulate and kill cancer cells.

Computed tomography (CT or CAT) scan—Using X rays taken from many angles and computer modeling, CT scans help locate and size tumors and provide information on whether they can be surgically removed.

Fractionation—A procedure for dividing a dose of radiation into smaller treatment doses.

Gamma rays—Short wavelength, high energy electromagnetic radiation emitted by radioactive substances.

Hodgkin's disease—Cancer of the lymphatic system, characterized by lymph node enlargement and the presence of a large polyploid cells called Reed-Sternberg cells.

Magnetic resonance imaging (MRI)—MRI uses magnets and radio waves to create detailed cross-sectional pictures of the interior of the body.

Stereotactic—Characterized by precise positioning in space. When applied to radiosurgery, stereotactic refers to a system of three-dimensional coordinates for locating the target site.

Fatigue frequently starts after the second week of therapy and may continue until about two weeks after the therapy is finished. Patients may need to limit their activities, take naps, and get extra sleep at night.

Patients should see their oncologist (cancer doctor) at least once within the first few weeks after their final radiation treatment. They should also see an oncologist every six to twelve months for the rest of their lives so they can be checked to see if the tumor has reappeared or spread.

Risks

Radiation therapy can cause **anemia**, nausea, vomiting, **diarrhea**, hair loss (alopecia), skin burn, sterility, and rarely death. However, the benefits of radiation therapy almost always exceed the risks. Patients should discuss the risks with their doctor and get a second opinion about their treatment plan.

Normal results

The outcome of radiation treatment varies depending on the type, location, and stage of the cancer. For some cancers such as Hodgkin's disease, about 75% of the patients are cured. **Prostate cancer** also responds well to radiation therapy. Radiation to painful bony metastases is usually a dramatically effective form of pain control. Other cancers may be less sensitive to the benefits of radiation.

Resources

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American Cancer Society. 1599 Clifton Rd. NE, Atlanta GA 30329-4251. (800) ACS-2345. <http://www.cancer.org>.

International Radiosurgery Support Association (IRSA). 3005 Hoffman Street, Harrisburg, PA 17110. (717) 260-9808. <www.irsa.org>.

National Association for Proton Therapy. 7910 Woodmont Ave., Suite 1303, Bethesda, MD 20814. (301) 913-9360. <http://www.proton-therapy.org/Default.htm.>

OTHER

Radiation Therapy and You. A Guide to Self-Help During Treatment. National Cancer Institute CancerNet Information Service. <http://cancernet.nci.nih.gov>.

Lorraine Lica
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Radical neck dissection

Definition

Radical neck dissection is an operation used to remove cancerous tissue in the head and neck.

Purpose

The purpose of radical neck dissection is to remove lymph nodes and other structures in the head and neck that are likely or proven to be malignant. Variations on neck dissections exist depending on the extent of the cancer. A radical neck dissection removes the most tissue. It is done when the cancer has spread widely in the neck. A modified neck dissection removes less tissue, and a selective neck dissection even less.

Precautions

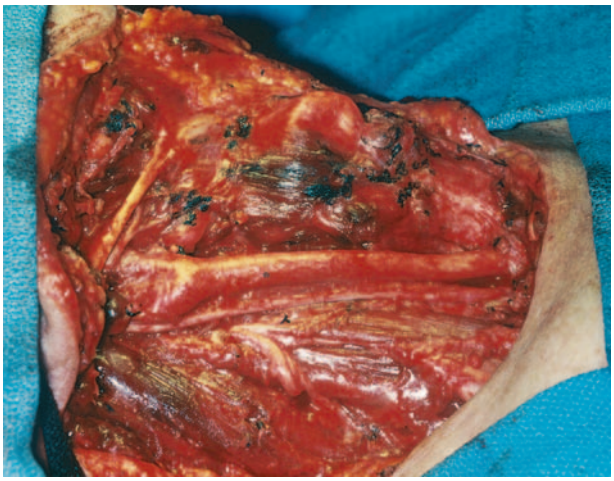
This operation should not be done if cancer has metastasized (spread) beyond the head and neck, or if the cancer has invaded the bones of the cervical vertebrae (the first seven vertebrae of the spinal column) or the skull. In these cases, the surgery will not effectively contain the cancer.

Description

Cancers of the head and neck (sometimes inaccurately called throat cancer) often spread to nearby tissues and into the lymph nodes. Removing these structures is one way of controlling the cancer.

Of the six hundred lymph nodes in the body, about 200 are in the neck. Only a small number of these are removed during a neck dissection. In addition, other structures such as muscles, veins, and nerves may be removed during a radical neck dissection. These include the sternocleidomastoid muscle (one of the muscles that functions to flex the head), internal jugular (neck) vein, submandibular gland (one of the salivary glands), and the spinal accessory nerve (a nerve that helps control speech, swallowing and certain movements of the head and neck). The goal is always to remove all the cancer but to save as many components surrounding the nodes as possible.

Radical neck dissections are done in a hospital under general anesthesia by a head and neck surgeon. An incision is made in the neck, and the skin is pulled back to reveal the muscles and lymph nodes. The surgeon is guided in what to remove by tests done prior to surgery and by examination of the size and texture of the lymph nodes.



A radical neck surgery in progress. *(Custom Medical Stock Photo. Reproduced by permission.)*

Preparation

Radical neck dissection is a major operation. Extensive tests are done before the operation to try to determine where and how far the cancer has spread. These may include lymph node biopsies, CT (**computed tomography**) scans, magnetic resonance imaging (MRI) scans, and barium swallows. In addition, standard pre-operative blood and liver function tests are performed, and the patient will meet with an anesthesiologist before the operation. The patient should tell the anesthesiologist about all drug allergies and all medication (prescription, non-prescription, or herbal) that he or she is taking.

Aftercare

A person who has had a radical neck dissection will stay in the hospital several days after the operation, and sometimes longer if surgery to remove the primary tumor was done at the same time. Drains are inserted under the skin to remove the fluid that accumulates in the neck area. Once the drains are removed and the incision appears to be healing well, patients are usually discharged from the hospital, but will require follow-up doctor visits. Depending on how many structures are removed, a person who has had a radical neck dissection may require physical therapy to regain use of the arm and shoulder.

Risks

The greatest risk in a radical neck dissection is damage to the nerves, muscles, and veins in the neck. Nerve damage can result in numbness (either temporary

KEY TERMS

Barium swallow—Barium is used to coat the throat in order to take x-ray pictures of the tissues lining the throat.

Computed tomography (CT or CAT) scan—Using x rays taken from many angles and computer modeling, CT scans help size and locate tumors and provide information on whether they can be surgically removed.

Lymphatic system—Primary defense against infection in the body. The tissues, organs, and channels (similar to veins) that produce, store, and transport lymph and white blood cells to fight infection.

Lymph nodes—Small, bean-shaped collections of tissue found in lymph vessels. They produce cells and proteins that fight infection and filter lymph. Nodes are sometimes called lymph glands.

Magnetic resonance imaging (MRI)—MRI uses magnets and radio waves to create detailed cross-sectional pictures of the interior of the body.

Malignant—Cancerous. Cells tend to reproduce without normal controls on growth and form tumors or invade other tissues.

Metastasize—Spread of cells from the original site of the cancer to other parts of the body where secondary tumors are formed.

or permanent) to different regions on the neck and loss of function (temporary or permanent) to parts of the neck, throat, and shoulder. The more extensive the neck dissection, the more function the patient is likely to lose. As a result, it is common following radical neck dissection for a person to have stooped shoulders, limited ability to lift the arm, and limited head and neck rotation and flexion due to the removal of nerves and muscles. Other risks are the same as for all major surgery: potential bleeding, infection, and allergic reaction to anesthesia.

Normal results

Normal lymph nodes are small and show no cancerous cells under the microscope.

Abnormal results

Abnormal lymph nodes may be enlarged and show malignant cells when examined under the microscope.

QUESTIONS TO ASK THE DOCTOR

- What tests will you do to determine if my cancer has spread?
- Which parts of my neck will be removed?
- How will a radical neck dissection affect my daily activities after recovery?
- What is the likelihood that all my cancer can be removed with a radical neck dissection?
- Are the lymph nodes on one or both sides of my neck involved?
- What will my appearance be like after surgery?
- How will my speech and breathing be affected?

Resources

ORGANIZATIONS

American Cancer Society. National Headquarters, 1599 Clifton Road NE, Atlanta, GA 30329. (800) ACS-2345). <http://www.cancer.org>.

Cancer Information Service. National Cancer Institute, Building 31, Room 10A19, 9000 Rockville Pike, Bethesda, MD 20892. (800) 4-CANCER. <http://www.nci.nih.gov/cancerinfo/index.html>.

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Radiofrequency ablation

Definition

Radiofrequency ablation is a treatment that uses radio waves to create heat and directs the heat though a needle probe at cancer cells to destroy tumors.

Purpose

Radiofrequncy ablation (RFA) is minimally invasive, meaning it involves having to enter the body, but not as severely as major surgery. Because of this and its ability to create heat in a specific location, RFA is a good

treatment choice for patients with many types of cancer. RFA also has proven to be an excellent alternative for many patients who have not been able to receive surgery or other cancer therapy, or who have tried other cancer treatments that have failed. For example, some patients cannot have surgery because they have heart or lung conditions that make a long procedure under general anesthesia risky. In other cases, the type, characteristics, or location of the cancer make RFA a better option. The treatment is used not only to help treat cancer, but to ease pain in cancer patients, treat tumors that recur, and to treat some conditions other than cancer.

Liver tumors

One of the cancers treated most by RFA is cancer of the liver. In many cases, removing the tumor with surgery would not leave enough healthy tissue for the liver to still function. Liver tumors that spread (metastasize) from cancers that started somewhere else in the body also are good candidates for RFA. If a patient has several tumors spread out across the liver, surgeons cannot operate. RFA can eliminate the smaller tumors and a surgeon can follow up by operating on the larger tumor if necessary. In some cases, a previous attempt to treat the tumor, such as with **chemotherapy**, has failed and RFA is the next option. RFA also might be used to treat a tumor that has recurred.

Lung tumors

Some patients with lung cancer also are too ill to have conventional surgery or want to avoid the long recovery and possible complications of surgery. RFA once was thought useful only for early, small lung cancers. But research released in 2004 showed that it safely and effectively treated advanced lung cancer as well. The technique also may be used to treat cancer spread to the lung (lung metastases). Physicians also may use RFA to remove most of a tumor that is too large to remove with surgery. The process of making the tumor smaller is called debulking.

Kidney tumors

Many patients with kidney tumors have surgery, but some patients only have one kidney, making RFA the preferred treatment, since it helps spare the only kidney. As with other organs, RFA is an excellent alternative for patients who have conditions that might prevent them from having surgery or for whom recovery from surgery would be difficult. RFA for kidney (renal) cancer is an excellent choice for patients with more than one tumor, if the tumors are smaller than about 4 to 5 cm.

Bone cancer and pain

When cancer spreads to the bones, it can become very painful. Usually, RFA for bone cancer is not used to treat the cancer, but to relieve the pain associated with it. Physicians also may use RFA to relieve pain associated with other cancers by shrinking a tumor that is causing pain, particularly when the tumor has not responded to other treatments or cannot be reached or treated with surgery. This may be referred to as palliation or palliative care.

Other cancers

Researchers continue to find new uses for RFA to treat a number of cancers. For example, a 2004 report showed that RFA could assist with **lumpectomy** for **breast cancer** by giving the patient a cancer-free area around the site where the tumor is removed. RFA also improved cosmetic results. RFA is considered safe, predictable, and cheap when compared to many other treatments.

Precautions

RFA is safe for most patients, and generally can be used in place of surgery for patients who cannot withstand longer surgical procedures, complications, and recovery times. Still, physicians will discuss the benefits and risks of RFA with patients in advance. The procedure usually will require some anesthesia. A medical history and blood tests may rule out some patients or require them to adjust certain medications. Also, some tumors or cancers are not considered treatable with RFA. The number and size of tumors that can be treated in a particular organ may be limited.

Description

Radiofrequency refers to the radio waves, or form of electromagnetic energy, produced by an electrical generator used in the RFA. Electromagnetic energy already is present in the natural environment, as in visible light, microwaves, and radio waves. The energy from radiofrequency is safer than that from **x rays** because it is absorbed by living tissue as simple heat, which does not change the structure of the cells.

The patient lies on a table in an examination or surgical suite and becomes a sort of electrical circuit through which the radio waves pass. Grounding pads are placed on the patient's back or thighs. Most RFA procedures today are performed by an interventional radiologist. An interventional radiologist is a medical doctor who specializes in performing medical procedures that involved radiology to diagnose and treat disease. The radiologist usually uses ultrasound, but sometimes **computed tomography** (CT) or **magnetic**

KEY TERMS

Lumpectomy—Removal of a breast tumor (by surgery) with a limited amount of surrounding breast tissue.

Metastasize—To spread to distant sites. This is the term used when cancer from one organ or site moves to another area of the body and causes cancer in another area or organ.

Percutaneous—Through the skin.

Recur, recurrence—Cancer that happens again after time has passed.

resonance imaging (MRI) equipment and video monitors during the procedure to guide the way to the tumor.

Most interventional radiologists guide the small needle or probe that holds the current through the patient's skin and directly into the tumor. This is called the percutaneous method and will make for an easier recovery. Sometimes, a single needle electrode is used; at other times, one straight needle contains many curved needles that retract inside the main probe until its tip is positioned within the tumor. Once the physician has positioned the tumor, the electrodes can open up like an umbrella to deliver heat to a larger area.

The heat can be controlled by the physician. At temperatures above 113 degrees Fahrenheit, RFA "cooks" the tumor. During the procedure, the radiologist is using real-time imaging (ultrasound, CT, or MRI) to locate the cancerous tumor and guide the needle probe. A small needle can accurately heat a precise area. If a tumor is large, the radiologist may have to guide and reposition the probe several times to destroy the entire tumor. After destroying the tumor, the physician also will use the probe to heat and destroy a small margin or rim of healthy tissue around the cancerous tumor. This helps ensure that no single cancerous cell is left behind that can regrow. After the treatment is completed, a small bandage is placed over the probe insertion site. Each RFA treatment takes 15 to 30 minutes, but the entire procedure can take longer, depending on the number of tumors, tumor size, and location. For instance, the interventional radiologist may have to reposition the probe several times for one liver mass, then turn to a second smaller mass, for a total procedure time of 90 minutes. Some procedures can take up to three hours. RFA procedures are performed in hospitals, imaging centers, and physician offices. Most are done on an outpatient basis.

QUESTIONS TO ASK YOUR DOCTOR

- Why is radiofrequency ablation the best alternative for my cancer?
- What are the risks involved in the treatment?
- How many of these procedures have you performed?

Some pain can be associated with RFA, even with the percutaneous method. Most physicians will insert an intravenous (IV) line in the patient through which they will give anesthesia that makes the patient drowsy, but not completely out. This is often called "conscious sedation." In complex procedures, general anesthesia may be required with an anesthesiologist or nurse anesthetist present and monitoring the patient's vital signs. Sometimes, the physician uses a laparascope to introduce the probe. Although **laparoscopy** requires a tiny incision, it still is considered surgery. Some surgeons also use RFA on patients as part of general surgery. RFA sometimes is called radiofrequency thermal ablation.

Preparation

Before the RFA procedure, patients may have blood drawn for routine blood tests. The physician, nurse, or scheduler will provide preparation instructions that will include concerns about eating or drinking before the procedure. These instructions will depend on the type of anesthesia planned. Normally, patients will be told not to eat or drink eight hours (or after midnight) before the RFA procedure. Certain medications may need to be changed or stopped before the procedure. For example, blood thinners and aspirin may interfere with the procedure. A patient should reveal all current medications to the interventional radiologist or surgeon and follow preparation instructions.

Aftercare

The treatment team will move the patient to a recovery room following the procedure to allow anesthesia to wear off and to receive pain medication as needed. Some patients also have nausea and will receive medications and instructions for nausea and pain care before leaving the facility. Patients will have to remain in bed for the first few hours following the procedure, but seldom have to stay overnight from RFA. However, those having the procedure through surgery will require some hospital stay.

Once they return home, patients will be instructed to drink plenty of fluid and to take a prescription narcotic such as Percocet for the first day or two if pain continues. The physician likely will instruct patients not to drive a car or make important decisions for 24 hours after the procedure because of anesthesia effects. Excessive physical activity also is discouraged. However, most patients can resume normal diet, physical activity, and sexual activity within a few days of RFA.

Risks

The risks associated with radiofrequency ablation are relatively minor compared to those associated with many other cancer treatments, particularly surgery. However, no procedure is risk-free. Although rare, there is a risk of serious injury if the needle makes a hole (perforates) a nearby organ. If this happens, the patient may require surgery to repair the injury. There also is a minor risk of infection at the site where the probe is inserted. Patients may experience bruising or bleeding. Another possible complication from RFA to the lungs is air or gas in the chest cavity (pneumothorax), which may require a chest tube for a few days to drain the air. Finally, RFA is a complicated procedure and should be performed only by a physician trained specifically to do the procedure. Most interventional radiologists have extensive experience in these and similar procedures, but patients can check with accrediting societies, local medical societies and their primary care physicians and ask questions of the physician who will perform the procedure.

Normal results

Results vary, depending on the location, type, and size of tumor. Normally, scar tissue replaces the tumor cells destroyed by RFA and shrinks over a period of time. Patients should have no pain from the procedure after a few days.

Abnormal results

If pain continues for more than a few days, the patient should contact the physician. Some patients also develop flu-like symptoms and **fever** following RFA that can last for a few weeks. Bleeding after RFA has been reported. If it continues and is severe, the patient may have to return for an additional RFA procedure or surgery to control the bleeding. Sometimes, cancer recurs following RFA because tumors are so tiny they cannot be seen. Some patients will need another RFA procedure in the future.

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Teresa G. Odle

Radionuclide bone scan *see* **Nuclear medicine scans**

Radionuclide imaging *see* **Nuclear medicine scans**

Radiopharmaceuticals

Definition

Radiopharmaceuticals are radioactive substances that may be used to treat cancer.

Purpose

The common radiopharmaceuticals that are used in cancer treatment include:

- Chromic phosphate P 32 for the treatment of lung, ovarian, uterine, and prostate cancers
- Sodium iodide I 131 for treating certain types of **thyroid cancer**
- Strontium chloride Sr 89 for treating cancerous bone tissue
- Samarium Sm 153 lexidronam for treating cancerous bone tissue
- Sodium phosphate P 32 for treating cancerous bone tissue and other types of cancers.

Description

Radiopharmaceuticals used in cancer treatment are small, simple substances, containing a radioactive isotope or form of an element. They are targeted to specific areas of the body where cancer is present. Radiation emitted from the isotope kills cancer cells. These isotopes have short half-lives, meaning that most of the radiation is gone within a few days or weeks.

Chromic phosphate P 32 and sodium iodide I 131

Chromic phosphate P 32 is a salt of chromium and phosphoric acid, containing a radioactive form of the element phosphorous, ^{32}P. Its brand name is Phosphocol P 32. Chromic phosphate P 32 is used to treat fluid accumulations that can result from lung, ovarian, or uterine cancers. It is 50-80% effective in stopping fluid leakage from these organs. Chromic phosphate P 32 also is used to kill cancer cells that remain following surgery for uterine cancer. It may be used to treat ovarian or prostate cancers directly. The use of chromic phosphate P 32 is not combined with external beam radiation, but may be used in conjunction with **chemotherapy**.

Sodium iodide I 131, also called radioactive iodine or radioiodide, is a salt of sodium and a radioactive form of the element iodine, ^{131}I. Sodium iodide I 131 is taken up by the thyroid gland, which absorbs most of the iodine in the body. Sodium iodide I 131 can destroy the thyroid gland, with only minor effects on other parts of the body. It is used following surgery for thyroid cancer to destroy any remaining cancerous thyroid tissue, or to destroy thyroid cancer that has spread (metastasized) to lymph nodes or other tissues. Sodium iodide I 131 is a standard treatment for differentiated thyroid cancer that has spread to the neck and other parts of the body. Its use improves the survival rate for such patients. It is not clear whether radioiodide is beneficial for small cancers of the thyroid that have not metastasized to other tissues.

Bone metastasis

Several radiopharmaceuticals are used to treat cancerous tissue in the bone, particularly from **prostate cancer**. Most prostate cancer metastasizes to the bone and often this is the cause of death. When injected into a vein these radiopharmaceuticals accumulate in cancerous bone tissue and give off radiation that kills cancer cells and relieves pain in the majority of patients. These treatments are most effective for cancer that has metastasized to multiple bones. Sometimes these radiopharmaceuticals are used in conjunction with external beam radiation that is directed at the most painful areas.

Strontium chloride Sr 89 (strontium-89) is the most common radiopharmaceutical for treating bone cancer or prostate cancer that has metastasized to the bone. It is a salt of chlorine and a radioactive isotope of strontium, ^{89}Sr. Its brand name is Metastron. Men with advanced prostate cancer who are responding to chemotherapy appear to have a better chance of survival if bone metastases is treated with strontium-89 every six weeks in conjunction with a chemotherapy drug.

Samarium SM 153 lexidronam is a radioactive form of samarium, ^{153}Sm. The element is inside a small molecule called lexidronam. The brand name for samarium SM 153 lexidronam is Quadramet. It is used primarily to treat prostate cancer that has metastasized to the bone.

Sodium phosphate P 32 is a salt of sodium and phosphoric acid containing a radioactive form of the element phosphorous, ^{32}P. It is used primarily for breast and prostate cancers that have metastasized to the bone. It also may be used to treat other types of cancer.

Two other radioactive isotopes, rhenium 86 and rhenium 188, sometimes are used to treat bone **metastasis** from prostate cancer.

Recommended dosage

Dosages of radiopharmaceuticals vary with the individual and the type of treatment. Dosages of radioactive materials are expressed in units called millicuries.

Chromic phosphate P 32 is a suspension that is delivered through a catheter, or tube, inserted into the

sac surrounding the lungs, or into the abdominal or pelvic cavities. The usual dosage is 15-20 millicuries for abdominal administration and 10 millicuries for administration to the lung sac. Chromic phosphate P 32 also may be injected into the ovaries or prostate.

Sodium Iodide I 131 is taken by mouth as a capsule or a solution. The usual dose for treating thyroid cancer is 30-200 millicuries, depending on age and body size. Doses may be repeated. Treatment usually requires two to three days of hospitalization. For this therapy to be effective there must be high levels of thyroid-stimulating hormone (TSH, or thyrotropin) in the blood. This hormone can be injected prior to treatment.

Strontium-89 is injected into a vein. The usual dosage is 4 millicuries, depending on age, body size, and blood cell counts. Repeated doses may be required.

The usual dosage of samarium Sm 153 lexidronam is 1 millicurie per kg (0.45 millicurie per lb) of body weight, injected slowly into a vein. Repeated doses may be necessary. Because samarium Sm 153 lexidronam may accumulate in the bladder, it is important to drink plenty of liquid prior to treatment and to urinate often after treatment. This reduces the irradiation of the bladder.

The dosage of sodium phosphate P 32 depends on age, body size, blood cell counts, and the type of treatment. The usual dosages range from 1–5 millicuries. Repeated doses may be required.

Precautions

Some individuals may have an allergic reaction to strontium-89, samarium SM 153 lexidronam, or sodium phosphate P 32.

Radiopharmaceuticals usually are not recommended for use during pregnancy. It is recommended that women do not become pregnant for a year after treatment with sodium iodide I 131. Breast-feeding is not possible during treatment with radiopharmaceuticals.

Precautions before treatment with sodium iodide I 131

Foods containing iodine, such as iodized salt, seafoods, cabbage, kale, or turnips, should be avoided for several weeks prior to treatment with sodium iodide I 131. The iodine in these foods will be taken up by the thyroid, thereby reducing the amount of radioiodide that can be taken up. Radiopaque agents containing iodine sometimes are used to improve imaging on an **x ray**. A recent x-ray exam that included such an agent may interfere with the ability of the thyroid to take up radioiodide.

Diarrhea or vomiting may cause sodium iodide I 131 to be lost from the body, resulting in less effective treatment and the risk of outside contamination. Kidney disease may prevent the excretion of radioiodide, increasing the risk of side effects from the drug.

Precautions after treatment with radiopharmaceuticals

Strontium-89, samarium Sm 153 lexidronam, and large total doses of sodium iodide I 131 may temporarily lower the number of white blood cells, which are necessary for fighting infections. The number of blood platelets (important for blood clotting) also may be lowered. Precautions for reducing the risk of infection and bleeding include:

- avoiding people with infections
- seeking medical help at the first sign of infection or unusual bleeding
- using care when cleaning teeth
- avoiding touching the eyes or inside of the nose
- avoiding cuts and injuries

It is important to drink plenty of liquids and to urinate often after treatment with sodium iodide I 131. This flushes the radioiodide from the body. To reduce the risk of contaminating the environment or other people, the following procedures should be followed for 48–96 hours after treatment is sodium iodide I 131:

- avoiding kissing and sex
- avoiding the handling of another person's eating utensils, etc.
- avoiding close contact with others, especially pregnant women
- washing the tub and sink after each use
- washing hands after using or cleaning the toilet
- using separate washcloths and towels
- washing clothes, bed linens, and dishes separately
- flushing the toilet twice after each use

Strontium-89 and samarium Sm 153 lexidronam also are excreted in the urine. To prevent radioactive contamination, special measures should be followed for one week after receiving strontium-89 and for 12 hours after receiving samarium Sm 153 lexidronam:

- using a toilet rather than a urinal
- flushing the toilet several times after each use
- wiping up and flushing any spilled urine or blood
- washing hands after using or cleaning a toilet

KEY TERMS

Half-life—Length of time for the decay of one half of the radiation in a sample of a given radioactive isotope.

Isotopes—Forms of a chemical element that have the same number of protons (atomic number) but different numbers of neutrons and different atomic weights.

Lymph nodes—Small round glands, located throughout the body, that remove foreign organisms and debris from the lymphatic fluid.

Metastasis—Spread of cancer from its point of origin to other parts of the body, such as the bone.

Millicurie—Unit for measuring radioactivity; one millicurie is the quantity of a radioactive isotope that undergoes 3.7×10^{7} disintegrations per second.

Platelet—Blood component that aids in clotting.

Thyroid—Gland on each side of the trachea (windpipe) that secretes hormones to regulate metabolism and growth.

- washing soiled clothes and bed linens separately from other laundry.

Individuals with bladder control problems must take special measures following treatment to prevent contamination with radioactive urine.

Side effects

The more common side effects of chromic phosphate P 32 may include:

- loss of appetite (anorexia)
- abdominal cramps
- diarrhea
- nausea and vomiting
- weakness or fatigue

Less common but serious side effects of chromic phosphate P 32 may include:

- severe abdominal pain
- severe nausea and vomiting
- fever
- chills
- dry cough
- sore throat
- chest pain
- difficulty breathing
- bleeding or bruising

Side effects of treatment with sodium iodide I 131 are rare and temporary. However, they may include:

- loss of taste
- dry mouth (xerostomia)
- stomach irritation
- nausea and vomiting
- tenderness in the salivary glands or neck

Large total doses of radioiodine may cause infertility in men.

Flushing and transient increased **bone pain** are among the more common side effects of strontium-89.

Less common side effects of samarium Sm 153 lexidronam include:

- irregular heartbeat
- temporary increase in bone pain
- nausea and vomiting

Signs of infection due to low white blood cell counts after treatment with strontium-89, samarium Sm 153 lexidronam, or sodium iodide I 131 include:

- fever or chills
- cough or hoarseness
- lower back or side pain
- painful or difficult urination

Signs of low platelet count after treatment with strontium-89, samarium Sm 153 lexidronam, or sodium iodide I 131 include:

- bleeding or bruising
- black, tar-like stools
- blood in urine or stools
- tiny red spots on the skin

Side effects are rare with sodium phosphate P 32. However, for patients treated with sodium phosphate P 32 for bone pain, side effects may include:

- diarrhea
- fever
- nausea and vomiting

Anemia (low red blood cell count) or a decrease in the white blood cell count also are possible.

Since children and older adults are particularly sensitive to radiation, they may experience more side effects during and after treatment with radio- pharmaceuticals.

Interactions

Radiation therapy or anticancer drugs may increase the harmful effects of strontium-89 and samarium SM 153 lexidronam on the bone marrow. Medicines containing calcium may prevent strontium-89 from being taken up by bone tissue. Etidronate (Didronel, one of the so-called **bisphosphonates** that may be used to prevent or treat osteoporosis) may prevent samarium Sm 153 lexidronam from working effectively.

Margaret Alic, Ph.D.

Raloxifene

Definition

Raloxifene is a synthetic called an antiestrogen. It mimics the action of estrogen on the bones, but blocks the effects of estrogen on breast and uterine tissues.

Purpose

Raloxifene is a hormone therapy drug that protects against bone loss (osteoporosis) in postmenopausal women. During large studies of raloxifene's effectiveness against osteoporosis, researchers discovered that women taking the drug developed fewer breast cancers than women taking the placebo. Therefore, it is being considered as a drug used to fight **breast cancer**.

Description

In 1997 the United States Food and Drug Administration (FDA) approved raloxifene for use against bone loss (osteoporosis) in postmenopausal women. As of 2001, raloxifene (Evista) was being tested as a hormone therapy drug to reduce the risk and fight breast cancer in postmenopausal women. As of 2003, raloxifene was only approved for use in postmenopausal women. However, studies were looking at its effects in preventing cancer in all women and in lowering risk of fractures in women with osteopenia.

Raloxifene belongs to a family of compounds called **antiestrogens**. Antiestrogens are used in cancer therapy to inhibit the effects of estrogen on target tissues. Estrogen is a steroid hormone secreted by granulosa cells of a maturing follicle within the female ovary. Depending on the target tissue, estrogen can stimulate the growth of female reproductive organs and breast tissue, play a role in the female menstrual cycle, and protect against bone loss by binding to estrogen receptors on the outside of cells within the target tissue. Antiestrogens act selectively against the effects of estrogen on target cells in a variety of ways, thus they are called selective estrogen receptor modulators (SERMs).

Raloxifene selectively inhibits the effects of estrogen on breast tissue and uterine tissue, while selectively mimicking the effects of estrogen on bone (by increasing bone mineral density). Its effects on breast and uterine tissue are thought to make raloxifene an excellent therapeutic agent against breast cancer and uterine cancer. Although researchers are unclear on exactly how raloxifene kills cancer cells, it is known to compete with estrogen by binding to estrogen receptors, therefore limiting the effects of estrogen on breast and uterine tissue. Raloxifene also may be involved in other anti-tumor activities affecting oncogene expression, promotion of apoptosis, and growth factor secretion.

In 2000 the STAR (Study of **Tamoxifen** and Raloxifene) study began. The purpose of this double-blind study was to evaluate the use of tamoxifen (another type of SERM) and raloxifene over a five year period in 22,000 postmenopausal women 35 years or older who are at high risk for developing breast cancer. The study will evaluate both the effectiveness and degree of side effects to determine which drug is most beneficial.

Recommended dosage

Recommended dose for cancer treatment will emerge as clinical trials enter their final phases. Most studies, including the STAR trial, are using a total of 60 milligrams of raloxifene administered either once or twice (morning and night) each day with notable success. If a dosage is missed, patients should not double the next dosage. Instead, they should go back to their regular schedule and contact their doctor.

Precautions

Although raloxifene is only approved for use by women past the child bearing years, researchers emphasize that it is not recommended for women who are pregnant or breast feeding. In test animals, raloxifene caused birth defects and miscarriages. Although it is not known whether raloxifene is present in breast milk, it is possible that its presence may be toxic to infants. Further, this drug is not recommended for use in children.

KEY TERMS

Anticoagulant—An agent preventing the coagulation (clotting) of blood.

Apoptosis—A type of cell death where cells are induced to commit suicide.

Double-blind study—A study where neither the participant nor the physician know who has received the drug in question.

Granulosa cells—Cells that form the wall of the ovarian follicle.

Oncogene—A gene whose presence can cause cancer; these genes usually arise through mutation of a normal gene.

Ovarian follicle—Several layers of cells that surround a maturing egg in the ovary.

Thromboembolism—A blood clot that blocks a blood vessel in the cardiovascular system.

Patients at risk for the formation of thromboembolisms should use raloxifene with caution. Raloxifene can cause a higher risk of developing blood clots. Additionally, women experiencing liver disease will have a higher level of raloxifene in their blood system.

Side effects

Although raloxifene is usually well tolerated by patients, there are some side effects. Commonly reported side effects include mild nausea, vomiting, hot flashes, weight gain, **bone pain**, and hair thinning, which are not severe enough to stop therapy. Most of the side effect information regarding raloxifene comes from studies using it to counter osteoporosis where patients have not needed to take it over a long period of time. When studied for anticancer properties, raloxifene needs to be taken over a longer period of time. Since raloxifene's anticancer properties still are under investigation, researchers are not completely aware of all of the long term and potentially serious side effects. Researchers are aware that women taking raloxifene are three times more likely to develop thromboembolisms than women not taking raloxifene.

Interactions

The usefulness of raloxifene can be diminished if patients also are on estrogen supplements (such as Premarin, Estrace, Estratab, Climara, or Vivelle) and cholesterol-lowering cholestyramines (such as Questran). Cholestyramines decrease the absorption of raloxifene into the blood, while estrogen supplements increase the amount of estrogen competing with raloxifene for binding sites on target cells' estrogen receptors.

Raloxifene interferes with the anticoagulant effect of **warfarin** with severe consequences and even death. Patients using warfarin should make sure their physician is aware prior to commencing treatment with raloxifene.

See also Toremifene.

Resources

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Ranitidine *see* **Histamine 2 antagonists**

Receptor analysis

Definition

Receptor analysis is a diagnostic test that determines an important biological characteristic of the cells in a tumor—their response to normal growth factors.

Purpose

The goal of receptor analysis is to reveal whether the cancer cells in a tumor have specific molecules, termed receptors, on the cell surface. This test is routinely performed for **breast cancer**, as well as other tumors. Information as to the presence of these specific receptors can play a role in deciding the best course of treatment for a particular patient.

Precautions

Because this test is performed on a piece of tissue that has already been removed during a surgical or diagnostic procedure, it does not require any precautionary measures on behalf of the patient.

KEY TERMS

Anti-estrogen —A drug, for example tamoxifen, that prevents the hormone estrogen from influencing the behavior of specific types of cells.

Biopsy—A piece of tissue removed for diagnostic examination.

Receptors—Molecules, usually found on the surface of a cell, that are required for cells to be influenced by hormones and other growth factors.

QUESTIONS TO ASK THE DOCTOR

- What fraction of the cells in my tumor has normal receptors?
- Do the results of the receptor assay on the biopsy of my tumor make me a candidate for anti-estrogen treatment?
- How do the results of the receptor assays on my tumor influence your decision as to my treatment and prognosis?

Description

The cancer cells found in tumors or in the blood of leukemia patients can differ in many ways, and to varying degrees from the corresponding cells in normal tissues and blood. In some respects, cancer treatment depends upon the differences in behavior between tumor and normal cells. For example, tumor cells often grow faster than normal (non-cancerous) cells. The changes that occur as normal cells become cancerous are progressive. As a tumor develops the cells generally become less similar to normal cells and behave in a biologically different way. Some cancer treatments make use of the ways that cancer cells in a tumor can be like cells in the normal surrounding tissue.

One the most fundamental ways in which the early stages of some cancers resemble healthy tissue is that the growth of the cells in the tumor responds to some of the same factors that control the growth of normal tissues. The most common example of this is the response of breast cancer cells to estrogen. During the normal menstrual cycle, the mammary glands respond to changes in the levels of two hormones, estrogen and progesterone. In many cases, the growth of breast cancer tumor cells also responds to the presence or absence of estrogen. The response of both normal and tumor cells to these hormones depends upon presence of molecules termed estrogen and progesterone receptors. If cells in a breast tumor have these receptors, it is possible to inhibit the growth of the cancer cells by preventing estrogen from stimulating their growth. This is generally accomplished through the use of anti-estrogen drugs such as **tamoxifen**.

Receptor analysis usually involves a special technique, called immunocytochemistry, to examine a small piece of the tumor tissue. A tissue section, a slice of the tumor, is placed on a glass microscope slide. These tissue sections, which are very similar to those used in the initial diagnosis of the patient's breast cancer, are incubated with antibody preparations that will react with estrogen and progesterone receptors. Special reagents that lead to a chemical reaction where these antibodies are bound produce a visible color in cells that have hormone receptors. A pathologist then looks at the section with a microscope to determine the percentage of tumor cells that are receptor-positive. This information can be used to decide whether a woman with breast cancer should be treated with anti-estrogens. In addition, the presence of estrogen receptors is itself an accepted prognostic indicator. Tumors that have high levels of estrogen receptors are generally less aggressive. Taken together with information as to the patient's age, the size and grade of the tumor, and whether or not there is lymph node involvement, it is possible for a doctor to have some idea as to the likelihood the patient will remain disease-free after initial treatment.

Estrogen receptor analysis is an important and generally accepted part of managing breast cancer. More recently, assays for other cell surface receptors have been explored and introduced for the management of breast and other cancers. Examples of these include androgen receptors in **prostate cancer** and epidermal growth factor receptor (EGFR) in a variety of cancers. In 2001 the most prominent example of a receptor assay, other than estrogen receptor analysis, was testing for a cell surface molecule designated HER2. Patients whose tumors express higher than normal amounts of HER2 are believed to have worse prognoses. However, these patients may be treated with a specific reagent, a monoclonal antibody, which is targeted toward the HER2 protein. Analysis for HER2 can be performed in a similar way to estrogen receptor immunocytochemical assays, currently marketed as the HercepTest, or by using a different type of test that directly examines the gene for HER2. Treatment with the monoclonal antibody to HER2 can improve the survival of patients who express higher-than-normal levels of HER2 in their tumor cells.

Risks

This test is performed on a piece of tissue that has been removed during the initial surgery or diagnostic procedure used to establish the nature of the tumor. It does not require any new surgery on the patient and, so, does not entail any risk to the patient.

Results

Receptor assays measure molecules that play normal and essential roles in the natural function of various tissues. Abnormal results depend upon the particular tissue and the type of cancer involved. The presence of the appropriate receptor, for example estrogen receptors in breast tumors, may be indicative that the cancer can be treated with compounds that can inhibit the growth of the cells that make up the tumor. In other cases, receptor assays may enable a doctor to know the origin of a tumor. That is, sometimes it is not possible for a pathologist to examine a **biopsy** and be certain what type of cancer a tumor represents. Knowing the identity of the receptors found on the tumor cells may then provide important information for establishing the diagnosis and best course of treatment for such patients.

Resources

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Reconstructive surgery

Definition

Reconstructive surgery is a type of plastic surgery performed to reshape abnormal structures of the body to improve function and appearance. Reconstructive surgery is different from cosmetic surgery, which is performed to reshape normal structures of the body to improve a patient's appearance and self-esteem.

Purpose

The goals of reconstructive surgery are to reshape abnormal structures of the body, to improve function, and/or to allow a person to have a more normal appearance. Abnormal structures of the body that are corrected during reconstructive surgery may be the result of birth defects, developmental abnormalities, trauma or injury, infection, tumors, or disease. The three most commonly performed reconstructive surgeries in the United States are tumor ablation (removal) and reconstruction, hand surgery, and breast reconstruction.

Precautions

Reconstructive surgery should not be performed on patients who are not healthy enough to withstand a surgical procedure performed under general anesthetic. People with severe diabetes, an autoimmune disorder such as AIDS, or a suppressed immune system should not undergo reconstructive surgery. This type of surgery is also contraindicated in patients with a history of excessive smoking, obesity, poor wound healing, abnormal scarring and/or a bleeding disorder. Women who are pregnant should not undergo reconstructive surgeries.

Patients who have received recent irradiation treatments (generally within the last three to six months) should not undergo surgical procedures involving these tissues. Recently irradiated tissue is highly prone to infection and has poorer wound healing.

In some cases, after tumor removal surgeries, it is necessary to monitor the affected tissue for redevelopment of the tumor. Patients requiring this type of postoperative surveillance should not undergo further reconstructive surgeries since these surgeries could obscure the results of imaging techniques (**x ray**, **computed tomography**, or **magnetic resonance imaging**) used to monitor tumor recurrence.

Patients with an allergy to collagen, beef, or beef products should not receive collagen injections.

Description

The most commonly performed reconstructive surgeries of cancer patients are breast reconstruction, laceration repair, scar revision, and tumor removal.

Breast reconstruction

Breast reconstruction surgeries can be performed as part of the procedure to remove the breast (immediate **mastectomy**). They may also be performed as a separate procedure after recuperation from a mastectomy

(delayed). There are two types of breast reconstruction: autogenous free flap reconstruction and breast implants.

Autogenous free flap reconstructions use tissue from another part of the body to form the reconstructed breast. This category of breast reconstruction includes the techniques called TRAM (transverse rectus abdominis myocutaneous), LD (latissimus dorsi), VRAM (vertical rectus abdominis myocutaneous), and DIEP (deep inferior epigastric perforator) flaps. These names refer to the location from which the tissue for reconstruction is taken. As of 2001 TRAM, in which tissue is taken from the abdominal region, is the most common breast reconstruction procedure in the United States. As of 2004, DIEP is preferred when the reconstruction involves both breasts.

Breast implants involve the placement of an artificial object in the body to simulate the shape and size of the natural breast. The implant is most commonly a saline (salt water) or silicone-filled bag. Because of the health problems reported by many women after silicone breast implants, this technique is no longer as widespread as it once was, particularly for reconstructive surgeries.

A technique that is still in the experimental stage is breast tissue engineering, which seeks to use a relatively small amount of the patient's own adipose (fatty) tissue to create a larger volume of material that could be used to reconstruct the breast. As of 2004 one of the limitations on breast reconstruction is the need to use fairly large amounts of adipose tissue from the patient's body.

Breast reconstruction usually involves more than one operation; in fact the average number of secondary procedures required is four for reconstruction of one breast and 5.5 for reconstruction of both breasts. The factors that complicate breast reconstruction include delaying the reconstruction after the mastectomy; the need for radiation therapy; and the presence of other risk factors affecting the patient's health.

Laceration repair

Laceration repair includes the repair of large wounds caused by the removal of large tumors or tumors associated with the skin. It also includes the surgical repair of wounds that fail to heal or heal improperly. Laceration repair can be subdivided into four general categories: direct closure, skin grafts, tissue expansion, and flap surgery.

Direct closure (stitches) is usually only performed on wounds that are not very deep beneath the surface of the skin and that have straight edges of skin on either side of the wound. The primary goal in direct closure is to provide a permanent closure of the wound with a minimum of scarring.

Skin grafts are used for wounds that are wide and difficult or impossible to close directly. This technique involves removing healthy skin from a location on the patient (the donor site) and using it to cover the wound site. The skin will grow back at the donor site but often leaves a color mismatch. The donor site is chosen to best match the color of the skin needed in the graft area.

Tissue expansion is used to grow extra skin by stretching skin near the site that will require the skin. A small inflatable balloon is placed under the skin next to the area where the skin will be removed. Over time, this balloon is slowly filled with salt water until the skin has grown to the required size. The surgical procedure that involves the loss of skin is then performed and closed with the extra skin that was formed during the tissue expansion process. The major advantage associated with tissue expansion is that the skin grown in this way remains connected to its original blood and nerve supply, so the risk of loss of sensation in the area of the wound is greatly diminished. Also, the scars that result from tissue expansion are generally less noticeable than those from skin grafts or skin flaps. A final advantage of this method is the near perfect match in color provided by this skin.

Flap surgery involves taking a section of living tissue, with its blood supply, from one part of the patient and moving it to the area where it is needed. In most flap surgeries, one end of the flap remains attached to its original blood supply so that it continues to be nourished as it grows to heal the wound. In cases where the flap is completely removed and transplanted to another part of the body, the surgery involves the reconnection of all the tiny blood vessels of the flap tissue to the blood vessels of the new location (microsurgery). Flap surgery has the advantage of being able to restore both form and function to areas of the body that have lost skin, fat, muscle, and/or skeletal support. The most commonly performed flap surgeries are the autogenous breast reconstructions discussed above. But, this procedure is used throughout the body with a great amount of success.

Scar revisions

Many cancer patients have scarring that results from their particular form of cancer or from the number or severity of surgical procedures or radiation that they have undergone. In some of these cases, surgeries to minimize or reshape the scar, or scars, may be undertaken. Most physicians will recommend that a scar be allowed to heal for at least one year prior to a recommendation of scar revision. But, in extreme cases of loss of mobility, increased sensitivity, or inflamed and irritable scars that do not respond to topical steroid creams, this timetable may be shortened.

KEY TERMS

Cosmetic surgery—A form of plastic surgery that is performed to alter normal tissue to improve the appearance of that tissue.

Flap surgery—A procedure in which a portion of living tissue is moved from one part of a patient's body to another to restore shape and/or function to the targeted location.

Plastic surgery—A type of surgery that is performed to alter the physical characteristics of a patient. This medical discipline is subdivided into cosmetic surgery and reconstructive surgery.

Reconstructive surgery—A form of plastic surgery that is performed to repair or reshape abnormally formed tissue to improve the form and/or function of that tissue.

Scar revision—A surgical procedure that attempts to diminish the physical appearance of a scar. This procedure is also used to add flexibility and range of motion to joints and muscles that were previously hindered by a particular scar.

QUESTIONS TO ASK THE DOCTOR

- What are alternatives to this surgical procedure?
- What will the scars look like and can I expect them to decrease over time?
- How many reconstructions have you performed previously and may I see examples of the results or talk to former patients?
- Will this procedure be covered by my insurance?
- How long will the pre-operation waiting period, the hospital stay, and the recovery procedure be?

Unless proof of the scar contributing to a medical condition or a decrease in physical function can be shown, scar revision surgery is considered by most insurance companies to be a cosmetic surgery that is not covered as an insurance benefit. The most common reason for scar revision to be classified as a reconstructive rather than a cosmetic procedure is a loss of mobility of muscles or joints caused by the scar.

The most common procedure for scar revision is called Z-plasty. In this procedure, the old scar is removed and the two sides of the wound are cut into a z-shape that is designed to follow the natural lines and contours of the surrounding skin. This z-shaped wound is then closed with stitches. Other scar revision procedures include skin grafts and flap surgeries. Z-plasty is the least likely of these procedures to be covered by insurance.

Tumor removal

The surgical procedure used to remove a tumor will be chosen by the surgeon based on the type and size of the tumor. Other factors influencing the surgical technique chosen for tumor removal include: the location of the tumor within the body; the potential for recurrence of the tumor at this, or another, location in the body; and, the stage of development of both the tumor itself and the underlying cancer.

Skin cancers are generally removed by a cutting out (excision) of the cancerous portion of skin, with the wound closed by stitches or left to heal on its own. In cases of large or spreading skin cancers, major surgery involving skin grafts or flap surgeries may be required. For skin cancers in the facial area, **Moh's surgery** with primary or flap closure may be performed.

Preparation

The preparation for a reconstructive surgery depends on the type of surgery that is to be performed. Some reconstructive surgeries can be performed on an outpatient basis. These procedures require only a local anesthetic and very little patient preparation other than counseling about the risks, possible achievable outcomes, and alternatives to the surgery. Other reconstructive surgeries are considered major operations. These require hospitalization, a general anesthetic and much more extensive counseling and discussion of possible alternatives.

Prescription medications that may interfere with the performance of reconstructive surgery should be discontinued approximately two weeks prior to surgery, unless the surgeon advises otherwise. These medications include any medicines that may interfere with the anesthetic or that may increase bleeding. Over-the-counter medications, such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), should not be taken for at least one week prior to surgery unless approved by the doctor who will be performing the surgery. Patients undergoing surgeries that require a general anesthetic will be asked not to eat after midnight prior to the surgery and not to drink at least eight hours prior to surgery. The purpose of this is to ensure that the stomach is empty while the patient is unconscious. Otherwise, the stomach

contents could end up in the lungs, causing complications with the surgery or the recovery.

For procedures involving skin flaps, the patient may be asked to donate blood for possible use in a later transfusion.

In the case of tissue expansion procedures, the amount of time that will be required for the expansion of the tissue depends on the amount of tissue that must be grown to ensure an adequate closure of the wound. This may take a matter of days or several weeks.

Psychological and emotional preparation is important in reconstructive surgery to manage patient expectations. The patient should not expect cosmetically perfect results. Complete understanding of the limitations, as well as the benefits, of this surgery is necessary for a successful outcome.

Aftercare

The aftercare of a patient who has undergone a reconstructive surgery depends on the surgery, the overall health of the patient, and the wound care process. Some outpatient procedures require little aftercare other than a follow-up examination to determine the success of the procedure. Other procedures may require an extended hospitalization followed by extensive physical therapy. Smoking should be avoided, as it may cause delayed wound healing and higher risk of complications, including infection.

Procedures involving skin flaps or grafts require careful monitoring in the first days after surgery to ensure that proper blood circulation is taking place. Bandages and drainage tubes will remain in place for at least a day.

Scars may remain reddened and raised for a month or longer and may cause **itching**. Many people find that inflammation or severe itching from post-surgical scars is lessened, or completely eliminated, by topical treatments with vitamin E or steroidal creams.

After tumor removal, many patients require follow-up treatments and medical imaging to ensure that the tumor is not redeveloping.

Risks

The risks associated with all reconstructive surgeries are infection, bleeding, an unsightly scar, improper wound closure, and adverse reactions to anesthesia. Complications associated with flap reconstruction of the breasts include unusual firmness of the fatty tissue (fat necrosis), partial flap loss, fluid collection beneath the flap site, and muscle weakness (including abdominal hernias) at the donor site. For breast implants, complications include the formation of fibrous tissue around an implant, rupture or leakage of the implant, or movement of the implant from its intended location.

Normal results

The normal result of a reconstructive surgery is a patient who has an improved ability to function and/or an improved **body image** as a result of the surgery. A normal result also depends on the patient's realistic goals and expectations. The patient should understand that the feeling and appearance of the reconstructed area will be improved, not fully restored to an unaffected state.

Abnormal results

An abnormal result of a reconstructive surgery is a patient who suffers long-lasting health complications as a result of the surgery. Another abnormal result is a patient who suffers a degradation in the ability to function and/or has a loss of self-confidence caused by the loss of sensation or scarring that may accompany such procedures.

See also Breast cancer.

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ORGANIZATIONS

American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS). 310 South Henry Street, Alexandria, VA 22314. (703) 299-9291. <www.facemd.org>.

American Society of Plastic Surgeons Plastic Surgery Educational Foundation. 444 E. Algonquin Rd., Arlington

Heights, IL 60005. (888) 4-PLASTIC. <http://www.plasticsurgery.org>.

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Rectal cancer

Definition

The rectum is the portion of the large bowel that lies in the pelvis, terminating at the anus. Cancer of the rectum is the disease characterized by the development of malignant cells in the lining or epithelium of the rectum. Malignant cells have changed such that they lose normal control mechanisms governing growth. These cells may invade surrounding local tissue or they may spread throughout the body and invade other organ systems.

Description

The rectum is the continuation of the colon (part of the large bowel) after it leaves the abdomen and descends into the pelvis. It is divided into equal thirds: the upper, mid, and lower rectum.

The pelvis and other organs in the pelvis form boundaries to the rectum. Behind, or posterior to the rectum is the sacrum (the lowest portion of the spine, closest to the pelvis). Laterally, on the sides, the rectum is bounded by soft tissue and bone. In front, the rectum is bounded by different organs in the male and female. In the male, the bladder and prostate are present. In the female, the vagina, uterus, and ovaries are present.

The upper rectum receives its blood supply from branches of the inferior mesenteric artery from the abdomen. The lower rectum has blood vessels entering from the sides of the pelvis. Lymph, a protein-rich fluid that bathes the cells of the body, is transported in small channels known as lymphatics. These channels run with the blood supply of the rectum. Lymph nodes are small filters through which the lymph flows on its way back to the blood stream. Cancer spreads elsewhere in the body by invading the lymph and vascular systems.

When a cell or cells lining the rectum become malignant, they first grow locally and may invade partially or totally through the wall of the rectum. The tumor here may invade surrounding tissue or the organs that bound it, a process known as local invasion. In this process, the tumor penetrates and may invade the lymphatics or the capillaries locally and gain access to the circulation in this way. As the malignant cells work their way to other areas of the body, they again become locally invasive in the new area to which they have spread. These tumor deposits, originating in the primary tumor in the rectum, are then known as **metastasis**. If metastases are found in the regional lymph nodes, they are known as regional metastases. If they are distant from the primary tumor, they are known as distant metastases. The patient with distant metastases may have widespread disease, also referred to as systemic disease. Thus the cancer originating in the rectum begins locally and, given time, may become systemic.

By the time the primary tumor is originally detected, it is usually larger than one centimeter (about 3/8 inch) in size and has over one million cells. This amount of growth is estimated to take about three to seven years. Each time the cells double in number, the size of the tumor quadruples. Thus like most cancers, the part that is identified clinically is later in the progression than would be desired. Screening becomes a very important endeavor to aid in earlier detection of this disease.

Passage of red blood with the stool, (noticeable bleeding with defecation), is much more common in rectal cancer than that originating in the colon because the tumor is much closer to the anus. Other symptoms (constipation and/ or **diarrhea**) are caused by obstruction and, less often, by local invasion of the tumor into pelvic organs or the sacrum. When the tumor has spread to distant sites, these metastases may cause dysfunction of the organ they have spread to. Distant metastasis usually occurs in the liver, less often to the lung(s), and rarely to the brain.

Demographics

There are about 36,500 cases of rectal cancer diagnosed per year in the United States. Together, colon and rectal cancers account for 10% of cancers in men and 11% of cancers in women. It is the second most common site-specific cancer affecting both men and women. Nearly 57,000 people died from colon and rectal cancer in the United States in 2003. In recent years the incidence of this disease is decreasing very slightly, as has the mortality rate. It is difficult to tell if the decrease in mortality reflects earlier diagnosis, less death related to the actual treatment of the disease, or a combination of both factors.

Cancer of the rectum is felt to arise sporadically in about 80% of those who develop the disease. About 20% of cases probably arise from genetic predisposition; some people have a family history of rectal cancer occur-

ring in a first-degree relative. Development of rectal cancer at an early age suggests a genetically transmitted form of the disease as opposed to the sporadic form.

Causes and symptoms

Causes of rectal cancer are probably environmental in sporadic cases (80%), and genetic in the heredity-predisposed (20%) cases. Since malignant cells have a changed genetic makeup, this means that in 80% of cases, the environment spontaneously induces change. Those born with a genetic predisposition are either destined to get the cancer, or it will take less environmental exposure to induce the cancer. Exposure to agents in the environment that may induce mutation is the process of **carcinogenesis** and is caused by agents known as carcinogens. Specific carcinogens have been difficult to identify; dietary factors, however, seem to be involved.

Rectal cancer is more common in industrialized nations. Dietary factors may be the reason. Diets high in fat, red meat, total calories, and alcohol seem to add to increased risk. Diets high in fiber are associated with a decreased risk. High-fiber diets may be related to less exposure of the rectal epithelium to carcinogens from the environment as the transit time through the bowel is faster with a high-fiber diet than with a low-fiber diet.

Age plays a definite role in rectal cancer risk. Rectal cancer is rare before age 40. This incidence increases substantially after age 50 and doubles with each succeeding decade.

There also is a slight increase of risk for rectal cancer in the individual who smokes.

Patients who suffer from an inflammatory disease of the colon known as ulcerative colitis are also at increased risk.

On chromosome 5 is the APC gene associated with familial adenomatous polyposis (FAP) syndrome. There are multiple mutations that occur at this site, yet they all cause a defect in tumor suppression that results in early and frequent development of **colon cancer**. This is transmitted to 50% of offspring and each of those affected will develop colon or rectal cancer, usually at an early age. Another syndrome, hereditary non-polyposis colon cancer (HNPCC), is related to mutations in any of four genes responsible for DNA mismatch repair. In patients with colon or rectal cancer, the p53 gene is mutated 70% of the time. When the p53 gene is mutated and ineffective, cells with damaged DNA escape repair or destruction, allowing the damaged cell to multiply. Continued replication of the damaged DNA may lead to tumor development. Though these syndromes (FAP and HNPCC) have a very high incidence of colon or rectal cancer, family history without the syndromes is also a substantial risk factor. When considering first-degree relatives, history of one with colon or rectal cancer raises the baseline risk from 2% to 6%; the presence of a second raises the risk to 17%.

The development of polyps of the colon or rectum commonly precedes the development of rectal cancer. Polyps are growths of the rectal lining. They can be unrelated to cancer, pre-cancerous, or malignant. Polyps, when identified, are removed for diagnosis. If the polyp, or polyps, are benign, the patient should undergo careful surveillance for the development of more polyps or the development of colon or rectal cancer.

Symptoms of rectal cancer most often result from the local presence of the tumor and its capacity to invade surrounding pelvic structure:

- bright red blood present with stool
- abdominal distention (stretching from internal pressure) bloating, inability to have a bowel movement
- narrowing of the stool, so-called ribbon stools
- pelvic pain
- unexplained weight loss
- persistent chronic **fatigue**
- rarely, urinary infection or passage of air in urine in males (late symptom)
- rarely, passage of feces through vagina in females(late symptom)

If the tumor is large and obstructing the rectum, the patient will not be evacuating stool normally and will get bloated and have abdominal discomfort. The tumor itself may bleed and, since it is near the anus, the patient may see bright red blood on the surface of the stool. Blood alone (without stool) may also be passed. Thus, hemorrhoids are often incorrectly blamed for bleeding, delaying the diagnosis. If **anemia** develops, which is rare, the patient will experience chronic fatigue. If the tumor invades the bladder in the male or the vagina in the female, stool will get where it doesn't belong and cause infection or discharge. (This condition is also rare.) Patients with widespread disease lose weight secondary to the chronic illness.

Diagnosis

Screening evaluation of the colon and rectum are accomplished together. Screening involves physical exam, simple laboratory tests, and the visualization of the lining of the rectum and colon. X rays (indirect visualization) and endoscopy (direct visualization) are used to visualize the organs' lining.

The physical examination involves the performance of a digital rectal exam (DRE). At the time of this exam, the physician checks the stool on the examining glove with a chemical to see if any occult (invisible), blood is present. At home, after having a bowel movement, the patient is asked to swipe a sample of stool obtained with a small stick on a card. After three such specimens are on the card, the card is then easily chemically tested for occult blood. These exams are accomplished as an easy part of a routine yearly physical exam.

Proteins are sometimes produced by cancers and these may be elevated in the patient's blood. When this occurs the protein produced is known as a tumor marker. There is a tumor marker for cancer of the colon and rectum; it is known as carcinoembryonic antigen, (CEA). Unfortunately, this may be made by other **adenocarcinomas** as well, or it may not be produced by a particular colon or rectal cancer. Therefore, screening by chemical analysis for CEA has not been helpful. CEA has been helpful in patients treated for colon or rectal cancer if their tumor makes the protein. It is used in a follow-up role, not a screening role.

Direct visualization of the lining of the rectum is accomplished using a scope or endoscope. The physician introduces the instrument into the rectum and is able to see the epithelium of the rectum directly. A simple rigid tubular scope may be used to see the rectal epithelium; however, screening of the colon is done at the same time. The lower colon may be visualized using a fiberoptic flexible scope in a procedure known as flexible **sigmoidoscopy**. When the entire colon is visualized, the procedure is known as total **colonoscopy**. Each type of endoscopy requires pre-procedure preparation (evacuation) of the rectum and colon.

The American Cancer Society has recommended the following screening protocol for colon and rectal cancers those over age 50:

- yearly fecal occult blood test
- flexible sigmoidoscopy at age 50
- flexible sigmoidoscopy repeated every 5 years
- double contrast barium enema every five years
- colonoscopy every 10 years

If there are predisposing factors such as positive family history, history of polyps, or a familial syndrome, screening evaluations should start sooner.

Evaluation of patients with symptoms

When patients visit their physician because they are experiencing symptoms that could possibly be related to colon or rectal cancer, the entire colon and rectum must be visualized. Even if a rectal lesion is identified, the entire colon must be screened to rule out a syndromous polyp or cancer of the colon. The combination of a flexible sigmoidoscopy and double contrast **barium enema** may be performed, but the much-preferred evaluation of the entire colon and rectum is that of complete colonoscopy. Colonoscopy allows direct visualization, photography, as well as the opportunity to obtain a **biopsy**, (a sample of tissue), of any abnormality visualized. If, for technical reasons the entire colon is not visualized endoscopically, a double contrast barium enema should complement the colonoscopy. A patient who is identified to have a problem in one area of the colon or rectum is at greater risk to have a similar problem in another area of the colon or rectum. Therefore the entire colon and rectum need to be visualized during the evaluation.

The diagnosis of rectal cancer is actually made by the performance of a biopsy of any abnormal lesion in the rectum. Many rectal cancers are within reach of the examiner's finger. Identifying how close to the anus the cancer has developed is important in planning the treatment. Another characteristic ascertained by exam is whether the tumor is mobile or fixed to surrounding structure. Again, this will have implications related to primary treatment. As a general rule, it is easier to identify and adequately obtain tissue for evaluation in the rectum as opposed to the colon. This is because the lesion is closer to the anus.

If the patient has advanced disease, areas where the tumor has spread, such as the liver, may require biopsy. Such biopsies are usually obtained using a special needle under local anesthesia.

Once a diagnosis of rectal cancer has been established by biopsy, in addition to the physical exam, an **endorectal ultrasound** will be performed to assess the extent of the disease. For rectal cancer, endorectal ultrasound is the most preferred method for staging both depth of tumor penetration and local lymph node status. Endorectal ultrasound:

- differentiates areas of invasion within large rectal adenomas that may appear benign
- determines the depth of tumor penetration into the rectal wall
- determines the extent of regional lymph node invasion, thereby determining the metastatic status
- can be combined with other tests (chest x rays and **computed tomography** scans, or CT scans) to determine the extent of cancer spread to distant organs, such as the liver and/or the lungs

The resulting rectal cancer staging allows physicians to determine the need for—and order of—radiation, sur-

gery, and **chemotherapy**. In 2003, it was reported that magnetic resonance imaging (MRI) also may be useful in staging rectal cancer. MRI may help physicians determine if a tumor can be resected and what the risk of cancer recurrence will be.

Treatment team

Surgery, radiation treatment and chemotherapy are used in the therapy of cancer of the rectum. The extent of the primary tumor dictates whether surgery or radiation will be utilized first. When surgery is the primary local therapy, radiation often has an adjunctive role in helping to prevent local recurrence. Chemotherapy may be used as an adjunct also to decrease recurrence and improve overall survival. Thus, teamwork is required utilizing the skills of the surgeon and the radiation and medical oncologists.

Clinical staging, treatments, and prognosis

Once the diagnosis has been confirmed by biopsy and the endorectal ultrasound has been performed, the clinical stage of the cancer is assigned. The treating physicians use staging to plan the specific treatment protocol for the patient. In addition, the stage of the cancer at the time of presentation gives a statistical likelihood of the treatment outcome, (prognosis).

Clinical staging

Rectal cancer first invades locally and then progresses to spread to regional lymph nodes or to other organs. Stage is derived using the characteristics of the primary tumor, its depth of penetration through the rectum, local invasion into pelvic structure, and the presence or absence of regional or distant metastases. A CT scan of the pelvis is helpful in staging because tumor invasion into the sacrum or pelvic sidewalls may mean surgical therapy is not initially possible. On this basis, clinical staging is used to begin treatment. The pathologic stage is defined when the results of analyzing the surgical specimen are available. (typically stage I and II).

Rectal cancer is assigned stages I through IV, based on the following general criteria:

- Stage I: the tumor is confined to the epithelium (layer of cells covering the surface) or has not penetrated through the first layer of muscle in the rectal wall.
- Stage II: the tumor has penetrated through to the outer wall of the rectum or has gone through it, possibly invading other local tissue or organs.
- Stage III: Any depth or size of tumor associated with regional lymph node involvement.
- Stage IV: any of previous criteria associated with distant metastasis.

Treatments

SURGERY Surgical resection remains the mainstay of therapy in the treatment of rectal cancer. Stage I, II, and even suspected stage III disease are treated by surgical removal of the involved section of the rectum (resection) along with the complete vascular and lymphatic supply. However, because of the improvement in staging methods (principally endorectal ultrasound), many rectal cancers are now selected for pre-surgical treatment with radiation and, often, chemotherapy. The use of chemotherapy prior to surgery is known as neoadjuvant chemotherapy, and, in rectal cancer, neoadjuvant chemotherapy is used primarily for Stage II and Stage III rectal cancers. Following neoadjuvant treatment, the remaining tumor (often only a scar) is resected. In some cases, such neoadjuvant treatment avoids the need for permanent colostomy by major tumor shrinkage prior to surgery. Following surgery, chemotherapy is completed.

In other patients, surgical therapy alone (some small Stage I lesions) is followed by additional radiation and chemotherapy is selected. In a small group of patients with small, Stage I lesions, endoluminal radiation alone is performed as a curative treatment.

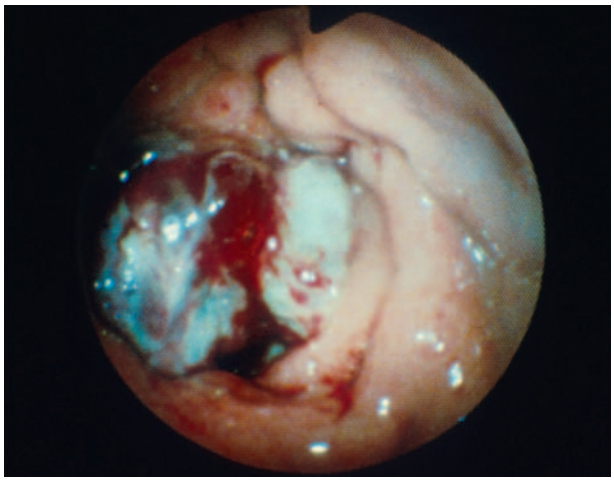
When determining primary treatment for rectal cancer, the surgeon's ability to reconnect the ends of the rectum must be considered. The pelvis is a confining space that makes surgical reconnection more difficult to do safely when the tumor is in the lower rectum. The upper rectum does not usually present a substantial problem to the surgeon restoring bowel continuity after the cancer has been removed. Mid-rectal tumors, especially in males where the pelvis is usually smaller than a woman's, may present technical difficulties in hooking the proximal bowel to the remaining rectum. Technical advances in stapling instrumentation have largely overcome these difficulties. If the anastomosis (hook-up) leaks postoperatively, infection can occur. In the past, this was a major cause of complications in resection of rectal cancers. Today, utilizing the stapling instrumentation, a hook-up at the time of original surgery is much safer. If the surgeon feels that the hook-up is compromised or may leak, a **colostomy** may be performed. A colostomy is performed by bringing the colon through the abdominal wall and sewing it to the skin. In these cases the stool is diverted away from the hook-up, allowing it to heal and preventing the infectious complications associated with leak. Later, when the hook-up has completely healed, the colostomy can be taken down and bowel continuity restored.

Stapling devices have allowed the surgeon to get closer to the anus and still allow the technical performance of a hook-up, but there are limits. It is generally felt that there should be at least three centimeters of normal rectum below the tumor or the risk of recurrence locally will be excessive. In addition, if there is no residual native rectum, the patient will not have normal sensation or control and will have problems with uncontrollable soilage, (**incontinence**). For these reasons, patients presenting with low rectal tumors may undergo total removal of the rectum and anus. This procedure is known as an abdominal-perineal resection. A permanent colostomy is performed in the lower left abdomen.

RADIATION As mentioned, for many late stage II or stage III tumors, **radiation therapy** can shrink the tumor prior to surgery. The other roles for radiation therapy are as an aid to surgical therapy in locally advanced disease that has been removed, and in the treatment of certain distant metastases. Especially when utilized in combination with chemotherapy, radiation used postoperatively has been shown to reduce the risk of local recurrence in the pelvis by 46% and death rates by 29%. Such combined therapy is recommended in patients with locally advanced primary tumors that have been removed surgically. Radiation has been helpful in treating effects of distant metastases, particularly in the brain. In very few cases, radiation alone may be the curative treatment for rectal cancer.

CHEMOTHERAPY Adjuvant chemotherapy, (treating the patient who has no evidence of residual disease but who is at high risk for recurrence), is considered in patients whose tumors deeply penetrate or locally invade (late stage II and stage III). If the tumor was not locally advanced, this form of chemotherapeutic adjuvant therapy may be recommended without radiation. This therapy is identical to that of colon cancer and leads to similar results. Standard therapy is treatment with 5-fluorouracil (5-FU, or fluorouracil) combined with **leucovorin** for a period of six to twelve months. 5-FU is an antimetabolite and leucovorin improves the response rate. Another agent, **levamisole** (which seems to stimulate the immune system) may be substituted for leucovorin. These protocols reduce the rate of recurrence by about 15% and reduce mortality by about 10%. The regimens have some toxicity but usually are tolerated fairly well.

Similar chemotherapy is administered for stage IV disease or if a cancer progresses and metastasis develops. Results show response rates of about 20%. A response is a temporary regression of the cancer in response to the chemotherapy. Unfortunately, these patients eventually succumb to the disease. **Clinical trials** have now shown that the results can be improved with the addition of another agent to this regimen. **Irinotecan** does not seem to increase toxicity but has improved response rates to 39%, added two to three months to disease-free survival, and prolonged overall survival by a little more than two months.



Rectal cancer seen through an endoscope. *(Custom Medical Stock Photo. Reproduced by permission.)*

Prognosis

Prognosis is the long-term outlook or survival after therapy. Overall, about 50% of patients treated for colon and rectal cancer survive the disease. As expected, the survival rates are dependent upon the stage of the cancer at the time of diagnosis, making early detection crucial.

About 15% of patients present with stage I disease, or are diagnosed with Stage I disease when they initially visit a doctor, and 85-90% survive. Stage II represents 20-30% of cases and 65-75% survive; 30-40% comprise the stage III presentation, of which 55% survive. The remaining 20-25% present with stage IV disease and are rarely cured.

Alternative and complementary therapies

Most alternative therapies have not been studied in clinical trials. Large doses of **vitamins**, fiber, and green tea are among therapies tried. A 2003 report on a large Harvard University study showed that people who took multivitamins for at least 15 years had a 34% reduction in risk of rectal cancer. Before initiating any alternative therapies, the patient should consult his or her physician to be sure that these therapies do

KEY TERMS

Adenocarcinoma—Cancer beginning in epithelial cells that line certain organs and have secretory properties.

Adjuvant therapy—Treatment involving radiation, chemotherapy (drug treatment), hormone therapy, or a combination of all three given after the primary treatment for the possibility of residual microscopic disease.

Anastomosis—Surgical re-connection of the ends of the bowel after removal of a portion of the bowel.

Anemia—The condition caused by too few circulating red blood cells, often manifest in part by fatigue.

Carcinogens—Substances in the environment that cause cancer, presumably by inducing mutations, with prolonged exposure.

Defecation—The act of having a bowel movement.

Epithelium—Cells composing the lining of an organ.

Lymphatics—Channels that are conduits for lymph.

Lymph nodes—Cellular filters through which lymphatics flow.

Malignant—Cells that have been altered such that they have lost normal control mechanisms and are capable of local invasion and spread to other areas of the body.

Metastasis—Site of invasive tumor growth that originated from a malignancy elsewhere in the body.

Mutation—A change in the genetic makeup of a cell that may occur spontaneously or be environmentally induced.

Occult blood—Presence of blood that cannot be appreciated visually.

Polyps—Localized growths of the epithelium that can be benign, pre-cancerous, or harbor malignancy.

Resect—To remove surgically.

Sacrum—Posterior bony wall of the pelvis.

Systemic—Referring to throughout the body.

not complicate or interfere with the recommended therapy.

Coping with cancer treatment

For those with familial syndromes causing colon cancer, genetic counseling may be appropriate. Psychological counseling may help anyone having trouble coping with a potentially fatal disease. Local cancer support groups are often identified by contacting local hospitals or the American Cancer Society.

The Colon Cancer Alliance offers online support at the following web page: <http://www.ccalliance.org/connect/support.html>.

Clinical trials

Clinical trials are scientific studies in which new therapies are compared to current standards in an effort to identify therapies that offer better results.

Agents being tested for efficacy in patients with advanced disease include **oxaliplatin** and CPT-11. Please see reference below for current information available from the National Cancer Institute regarding these clinical trials.

Prevention

There is not an absolute method for preventing colon or rectal cancer. An individual can lessen risk or identify the precursors of colon and rectal cancer. The patient with a familial history can enter screening and surveillance programs earlier than the general population. High-fiber diets and vitamins, avoiding obesity, and staying active lessen the risk. In fact, a 2003 report said that vigorous exercise (to the point of sweating or feeling out of breath) lowered risk of rectal cancer by nearly 40% compared to those who exercised less. Avoiding cigarettes and alcohol may be helpful. By controlling these environmental factors, an individual can lessen risk and to this degree prevent the disease.

By undergoing appropriate screening when uncontrollable genetic risk factors have been identified, an individual may be rewarded by the identification of benign polyps that can be treated as opposed to having these growths degenerate into a malignancy.

Special concerns

Polyps are growths of the epithelium of the colon. They may be completely benign, pre-malignant or cancerous. The association of colon and rectal cancers in patients with certain types of polyps is that many polyps begin as a benign growth and later acquire malignant characteristics. There are two types of polyps, pedunculated and sessile. This terminol-

ogy comes from their appearance; those that are pedunculated are on a stalk like a mushroom and the sessile polyps are broad based and have no stalk. Unless a pedunculated polyp gets large, malignant potential is very small. This type may also be easily removed at endoscopy. The sessile polyp is also known as a villous **adenoma**, as many as one-third of these harbor a malignancy. Therefore, the villous adenoma is considered premalignant. Sessile polyps may or may not be easily managed with the colonoscope and may need surgical removal because of their pre-malignant nature.

Polyps commonly present with occult blood in the stool. Since they are associated with the development of cancer, patients who have developed polyps need to enter a program of careful surveillance.

Elderly or debilitated patients with rectal cancers that seem localized may be treated by local destruction of the tumor through the anus. If the tumor is amenable to local resection or destruction by laser or cautery through the anus, the patient may be treated this way. This select group of patients may not be able to tolerate the standard therapy. Local control becomes the main issue while avoiding high-risk surgery and the inherent complications.

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Renal pelvis tumors

Definition

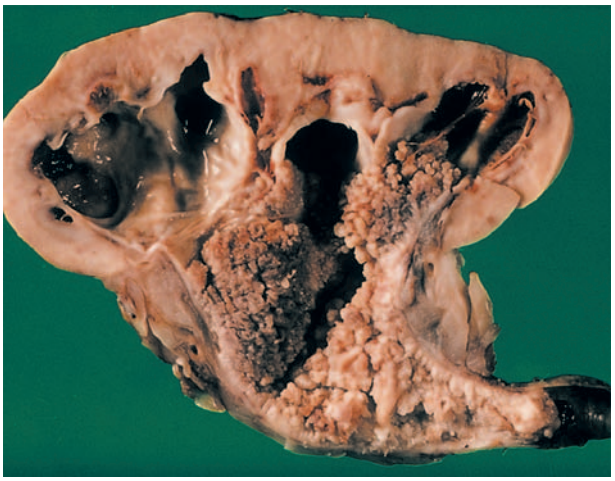
Renal pelvis tumors are rare kidney cancers appearing in a specific part of the kidney known as the pelvis of the kidney.

Description

The word "renal" means having to do with the kidneys. A part of each kidney in the human body is called the renal pelvis. The renal pelvis in each kidney is the portion of the collecting system that empties into the ureters (tubes that carry urine from the kidneys to the bladder).

Renal pelvis tumors usually appear after an earlier condition called renal papillary necrosis has already developed. The tumors may be composed of any one of several different types of cells. Most commonly, these tumors are of a type of cell known as a transitional cell carcinoma.

A transitional cell is intermediate between the flat squamous cell and the tall columnar cell. It is restricted to the epithelium (cellular lining) of the urinary bladder, ureters, and the renal pelvis. **Transitional cell carcinomas** have a wide range in their gross appearance depending on their locations. Some of these carcinomas are flat in appearance, some are papillary (small elevation), and others are in the shape of a node. Under the microscope, however, most of these carcinomas have a papillary-like look. There are three generally recognized grades of transitional cell carcinoma. The grade of the carcinoma is determined by particular characteristics found in the cells of the tumor. Transitional cell carcinoma typically affects the mucosa (the moist tis-



Transitional-cell carcinoma of the renal pelvis fills. *(Copyright Biophoto Associates, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

sue layer that lines hollow organs or the cavity of the body) in the areas where it originates— in this case, the kidney.

Demographics

Because statistics on these tumors are gathered with statistics on other kidney tumors, little information specific to tumors of the pelvic area of the kidney, as opposed to other areas of the kidney, is available. These tumors are relatively uncommon, however; they account for no more than 5% of cancers of the kidney and upper urinary tract. This percentage would indicate that 1785 Americans (1104 men and 684 women) were diagnosed with cancer of the renal pelvis in 2004 and 624 patients (394 men and 230 women) died of the disease. Renal pelvis cancers are more common in men than in women, as the statistics indicate, and appear most commonly in persons over the age of 65.

Causes and symptoms

The causes of renal cell cancer are not completely understood as of the early 2000s, but are thought to be related to the excretion of irritating substances in the urine. The appearance of renal pelvis tumors is often associated with a history of cigarette smoking and the overuse of certain pain medicines, as well as with a history of either kidney stones or **bladder cancer**. People who have worked in the rubber, paint, dye, printing, textile, and plastic industries and been exposed to certain chemicals are also at increased risk for this type of cancer. The risk is elevated, as well, for people with a rare kidney condition called Balkan nephropathy. This condition is more likely to affect people from Romania, Greece, Bulgaria, Serbia, Croatia, Bosnia-Herzegovina, and other countries included in the former Yugoslavia.

Approximately four out of five patients have symptoms of blood in the urine at the time of diagnosis. Approximately one out of three patients experiences pain in the side or lower back. Other frequent symptoms include urinary frequency or urgency, unintentional weight loss, brown or rusty-colored urine, and fatigue. Some patients may have no symptoms, while others may feel generally ill, visit the doctor for this general complaint, and have the cancer diagnosed at that time.

Diagnosis

Either urography or pyelography may be used to diagnose renal pelvis tumors. Both urography and pyelography are types of x-ray procedures that may be used to visualize portions of the urinary tract. The kidneys are part of the urinary tract. If urography is used, it is usually followed by **cystoscopy**. Cystoscopy involves the use of a medical instrument that permits the physician to look directly at portions of the urinary tract.

A newer technique is called ureteroscopy. Performing ureteroscopy increases the diagnostic accuracy doctors are able to attain. However, there is a risk that ureteroscopy may cause damage to some portion of the urinary tract. Therefore, ureteroscopy is usually reserved for those patients for whom unanswered questions remain after conventional diagnostic approaches have been completed.

The doctor may also order an **x ray** of the chest, a bone scan, and liver function tests to see whether the cancer has spread.

Clinical staging, treatments, and prognosis

Clinical staging

Tumor stage and grade provide important information on how an individual patient's renal pelvis tumor(s) will be treated and on the patient's prognosis. The primary tumor is staged on the basis of whether it remains superficial or has settled into the kidney. Patients with more superficial tumors have the best prognosis. However, even these patients may develop new tumors later.

Another factor important in determining treatment and prognosis is to determine the type and character of the individual cells that make up the tumor. Cells with a well-differentiated structure are associated with longer patient survival than cells with poorly differentiated structure.

Treatments

Surgery constitutes standard treatment for renal pelvis tumors. The surgical procedure is called a radical nephroureterectomy, and may involve the removal of a portion of the bladder as well. Some surgeons have attempted to perform part of the procedure through an endoscope rather than the standard open surgery, but early reports indicate that the rate of cancer recurrence is higher with endoscopic surgery.

Some patients should not receive surgical treatment for this cancer. Other patients should undergo a relatively more limited surgical procedure than the standard procedure—one in which less of the kidney is removed. Those who should be approached in the more limited way may include patients with only one single kidney, patients with cancer of both kidneys, and patients with Balkan nephropathy. In addition, patients who are in generally poor health may not be good candidates for surgery or may receive a limited surgical procedure.

Of course, patients with a single tumor comprised of well-differentiated cells are likely to have a better long-term outcome following a limited surgical procedure than are patients with several tumors comprised of poorly differentiated cells. It should be understood, however, that more limited procedures may involve a greater likelihood that the cancer will return.

Patients with Balkan nephropathy usually benefit from receiving the more limited procedure. These patients are at pre-existing risk of kidney failure because of the Balkan nephropathy; thus, the more of their kidneys preserved, the better for their future overall medical outcomes.

Some surgical procedures used for renal pelvis tumors are performed using a medical device that moves along the body channels used by urine. The use of this device in the treatment of renal pelvis tumors is, however, limited to extremely small tumors.

X-ray therapy may be used following a surgical procedure for renal pelvis tumors. In particular, it may be used if there is any evidence that tumor cells have affected any of the surrounding organs or if they are appearing in the lymph nodes. In addition, x-ray therapy may be recommended for patients who are at a higher-than-average risk for reappearance of cancer, for example, patients who are heavy smokers. Some authorities believe that additional studies are needed to clarify the effects of x-ray therapy for these patients.

Patients who experience pain related to renal pelvis tumors may receive x-ray treatment to control pain. Such treatment may be very effective. Patients with such pain may also benefit from **chemotherapy**.

KEY TERMS

Balkan nephropathy—A rare inherited kidney disorder that is associated with increased risk of developing renal pelvis tumors.

Cystoscopy—A medical procedure involving the use of a medical instrument that permits the physician to look directly at portions of the urinary tract.

Pyelography—A type of x-ray procedure applied to a portion of the urinary tract, of which the kidneys form part.

Renal—Having to do with the kidneys.

Renal papillary necrosis—A medical condition affecting the kidney and that increases a person's risk of developing a tumor of the renal pelvis.

Renal pelvis—That portion of the collecting system of the kidney that empties into the ureter.

Ureteroscopy—A diagnostic procedure that increases the diagnostic accuracy of the examination of possible renal pelvis tumors. Ureteroscopy may cause damage to some portion of the urinary tract. Therefore, ureteroscopy is usually reserved for those patients for whom unanswered questions remain after conventional diagnostic approaches have been completed.

Urography—A type of x-ray procedure applied to a portion of the urinary tract, of which the kidneys form part.

The patient with advanced renal pelvis cancer does not receive treatment that attempts to cure the disease. Rather, the treatment is palliative—it is used in an attempt to make the patient feel better and to improve the patient's quality of life. **Cisplatin** used alone has been shown to be an effective chemotherapy medicine in this situation.

It may, however, be preferable to use combination chemotherapy rather than cisplatin alone for patients with advanced disease, as a recent study demonstrated. The combination chemotherapy used in this study is the so-called M-VAC regimen, which consists of **methotrexate**, **vinblastine**, Adriamycin (**doxorubicin**), and cisplatin. This combination of medicines permitted patients both to live for a longer time without return of cancer and to live for a longer time overall.

Another combination of chemotherapy medicines studied for patients with advanced disease is the so-called CMV, which consists of cisplatin, methotrexate, and vinblastine.

QUESTIONS TO ASK THE DOCTOR

- How can I obtain supportive care so I come through this not only alive but with my family and emotional life intact?
- What sort of benefit and what sort of side effects might each of the available treatment options bring?
- Would you please inform me about treatment options and let me tell you about the priorities in my life so I can participate in forming a treatment plan?
- What is my prognosis?
- What are the chances, after I have completed treatment, that cancer may return? How frequently should I be checked so we can defeat any cancer that appears in the future?

It is important to examine the side effects that may accompany chemotherapy in these patients. Some of these side effects are severe, and a small percentage of patients treated using this modality die. Both the M-VAC and the CMV regimens help approximately half of patients and give some patients additional months of life.

Other newer medicines that have been tried as chemotherapy for patients with renal pelvis tumors and advanced disease are **paclitaxel** (Taxol) and **gemcitabine** (Gemzar). In 2005, it was questionable whether the use of either one of these medicines as single-drug chemotherapy produces superior results to the M-VAC or CMV regimens.

Prognosis

In terms of patient survival, almost all patients with superficial tumors composed of relatively well-differentiated cells live more than five years. In contrast, patients with poorly differentiated (abnormal in maturity and function) tumors that have invaded deep into the kidney and transplanted cells to other parts of the body may live only one year or less.

Approximately two out of five patients given limited surgical treatment for renal pelvis tumors will have new tumors develop. Therefore, it is important that these patients receive careful and regular follow-up. Some authorities recommend examinations for new tumors of and near the renal pelvis at three-, six-, nine-, twelve-, eighteen, and twenty-four months following surgery, and annually afterwards.

Coping with cancer treatment

Cancer patients need supportive care to help them come through the treatment period with physical and emotional strength in tact. Many patients experience feelings of **depression**, anxiety, and **fatigue**, and many experience nausea, vomiting, and other side effects during treatment. Studies have shown that these can be managed effectively if the patient discusses these issues with the treating physician.

Prevention

Smoking cessation is the most important step. In addition, persons working in the rubber, paint, dye, printing, textile, and plastic industries might speak with their doctor about whether they are at elevated risk of developing this cancer.

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Renal cell carcinoma *see* **Kidney cancer, renal cell**

Retinoblastoma

Definition

Retinoblastoma is a malignant tumor of the retina that occurs predominantly in young children.

Description

The eye has three layers, the sclera, the choroid, and the retina. The sclera is the outer protective white coating of the eye. The choroid is the middle layer and contains blood vessels that nourish the eye. The front portion of the choroid is colored and is called the iris. The opening in the iris is called the pupil. The pupil is responsible for allowing light into the eye and usually appears black. When the pupil is exposed to bright light it contracts (closes), and when it is exposed to low light conditions it dilates (opens) so that the appropriate amount of light enters the eye. Light that enters through the pupil hits the lens of the eye. The lens then focuses the light onto the retina, the innermost of the three layers. The job of the retina is to transform the light into information that can be transmitted to the optic nerve, which will transmit this information to the brain. It is through this process that people are able to see the world around them.

Occasionally a tumor, called a retinoblastoma, will develop in the retina of the eye. Usually this tumor forms in young children but it can occasionally occur in adults. Most people with retinoblastoma develop only one tumor (unifocal) in only one eye (unilateral). Some, however, develop multiple tumors (multifocal) in one or both eyes. When retinoblastoma occurs independently in both eyes, it is then called bilateral retinoblastoma.

Occasionally, children with retinoblastoma develop trilateral retinoblastoma. Trilateral retinoblastoma results from the development of an independent brain tumor that often forms in a part of the brain called the pineal gland. In order for retinoblastoma to be classified as trilateral, the tumor must have developed independently and not as the result of the spread of the retinal cancer. The prognosis for trilateral retinoblastoma is quite poor.

The retinal tumor which characterizes retinoblastoma is malignant, meaning that it can metastasize (spread) to other parts of the eye and eventually other parts of the body. In most cases, however, retinoblastoma is diagnosed before it spreads past the eye to other parts of the body (intraocular) and the prognosis is quite good. The prognosis is poorer if the cancer has spread beyond the eye (extraocular).

Retinoblastoma can be inherited or can arise spontaneously. Approximately 40% of people with retinoblastoma have an inherited form of the condition and approximately 60% have a sporadic (not inherited) form. Individuals with multiple independent tumors, bilateral retinoblastoma, or trilateral retinoblastoma are more likely to be affected with the inherited form of retinoblastoma.

Demographics

Approximately 1 in 15,000 to 1 in 30,000 infants in Western countries are born with retinoblastoma, making it the most common childhood eye cancer. It is, however, a relatively rare childhood cancer and accounts for approximately 3% of **childhood cancers**. The American Academy of Ophthalmology estimates that 300–350 cases of retinoblastoma occur in the United States each year.

Retinoblastoma is found mainly in children under the age of five but can occasionally be seen in older children and adults. Retinoblastoma is found in individuals of all ethnic backgrounds and is found equally frequently in males and females. The incidence of bilaterial retinoblastoma in the United States is thought to be slightly higher among black children than among either Caucasian or Asian American children.

Causes and symptoms

Causes

Retinoblastoma is caused by changes in or absence of a gene called RB1. RB1 is located on chromosome 13q14. Cells of the body, with the exception of the egg and sperm cells, contain 23 pairs of chromosomes. All of the cells of the body excluding the egg and the sperm cells are called the somatic cells. The somatic cells contain two of each chromosome 13 and therefore two copies of the RB1 gene. Each egg and sperm cell contains only one copy of chromosome 13 and therefore only contains one copy of the RB1 gene.

RB1 produces a tumor suppressor protein that normally helps to regulate the cell cycle of cells such as those of the retina. A normal cell of the retina goes through a growth cycle during which it produces new cells. Genes such as tumor suppressor genes tightly regulate this growth cycle.

Cells that lose control of their cell cycle and replicate out of control are called cancer cells. These undergo many cell divisions, often at a quicker rate than normal cells, and do not have a limited lifespan. A group of adjacent cancer cells can form a mass called a tumor. Malignant (cancerous) tumors can spread to other parts of the body. A malignant tumor of the retina (retinoblastoma) can result when just one retinal cell loses control of it cell cycle and replicates out of control.

Normally the tumor suppressor protein produced by RB1 prevents a retinal cell from becoming cancerous. Each RB1 gene produces tumor suppressor protein. Only one functioning RB1 gene in a retinal cell is necessary to prevent the cell from becoming cancerous. If both RB1 genes in a retinal cell become non-functional, then a retinal cell can become cancerous and retinoblastoma can result. An RB1 gene is non-functional when it is changed or missing (deleted) and no longer produces normal tumor suppressor protein.

Approximately 40% of people with retinoblastoma have inherited a nonfunctional or deleted RB1 gene from either their mother or father. Therefore, they have a changed/deleted RB1 gene in every somatic cell. A person with an inherited missing or non-functional RB1 gene will develop a retinal tumor if the remaining RB1 gene becomes changed or deleted in a retinal cell. The remaining RB1 gene can become non-functional when exposed to environmental triggers such as chemicals and radiation. In most cases, however, the triggers are unknown. Approximately 90% of people who inherit a changed or missing RB1 gene will develop retinoblastoma.

People with an inherited form of retinoblastoma are more likely to have a tumor in both eyes (bilateral) and are more likely to have more than one independent tumor (multifocal) in one or both eyes. The average age of onset for the inherited form of retinoblastoma is one year, which is earlier than the sporadic form of retinoblastoma. Although most people with the inherited form of retinoblastoma develop bilateral tumors, approximately 15% of people with a tumor in only one eye (unilateral) are affected with an inherited form of retinoblastoma.

A person with an inherited missing or non-functional RB1 gene has a 50% chance of passing on this abnormal gene to his or her offspring. The chance that their children will inherit the changed/deleted gene and actually develop retinoblastoma is approximately 45%.

Some people with retinoblastoma have inherited a non-functioning or missing RB1 gene from either their mother or father even though their parents have never developed retinoblastoma. It is possible that one parent has a changed or missing RB1 gene in every somatic cell but has not developed retinoblastoma because their remaining RB1 gene has remained functional. It is also possible that the parent had developed a retinal tumor that was destroyed by the body. In other cases, one parent has two normal RB1 genes in every somatic cell, but some of their egg or sperm cells contain a changed or missing RB1 gene. This is called gonadal mosaicism.

Retinoblastoma can also result when both RB1 genes become spontaneously changed or deleted in a retinal cell but the RB1 genes are normal in all the other cells of the body. Approximately 60% of people with retinoblastoma have this type of disease, called sporadic retinoblastoma. A person with sporadic retinoblastoma does not have a higher chance of having children with the disease. Their relatives do not have a higher risk of developing retinoblastoma themselves or having children who develop retinoblastoma. Sporadic retinoblastoma is usually unifocal and has an average age of onset of approximately two years.

Symptoms

The most common symptom of retinoblastoma is leukocoria. Leukocoria results when the pupil reflects a white color rather than the normal black or red color that is seen on a flash photograph. It is often most obvious in flash photographs since the pupil is exposed to a lot of light and the duration of the exposure is so short that the pupil does not have time to constrict. Children with retinoblastoma can also have problems seeing and this can cause them to appear cross-eyed (strabismus). People with retinoblastoma may also experience red, painful, and irritated eyes, inflamed tissue around the eye, enlarged pupils, and possibly different-colored eyes.

Diagnosis

Children who have symptoms of retinoblastoma are usually first evaluated by their pediatrician. The pediatrician will often perform a red reflex test to diagnose or confirm leukocoria. Prior to this test the doctor inserts medicated eye drops into the child's eyes so that the pupils will remain dilated and not contract when exposed to bright light. The doctor then examines the eyes with an ophthalmoscope, which shines a bright light into the eyes and allows the doctor to check for leukocoria. Leukocoria can also be diagnosed by taking a flash Polaroid

photograph of a patient who has been in a dark room for three to five minutes.

If the pediatrician suspects retinoblastoma on the basis of these evaluations, he or she will most likely refer the patient to an ophthalmologist (eye doctor) who has experience with retinoblastoma. The ophthalmologist will examine the eye using an indirect ophthalmoscope. The opthalmoscope shines a bright light into the eye, which helps the doctor to visualize the retina. This evaluation is usually done under general anesthetic, although some very young or older patients may not require it. Prior to the examination, medicated drops are put into the eyes to dilate the pupils, and anesthetic drops may also be used. A metal clip is used to keep the eyes open during the evaluation. During the examination, a cotton swab or a metal instrument with a flattened tip is used to press on the outer lens of the eye so that a better view of the front areas of the retina can be obtained. Sketches or photographs of the tumor as seen through the ophthalmoscope are taken during the procedure.

An ultrasound evaluation is used to confirm the presence of the tumor and to evaluate its size. Computed tomography (CT, or CAT, scan) is used to determine whether the tumor has spread outside of the eye and to the brain. Sometimes **magnetic resonance imaging** (MRI) is also used to look at the eyes, eye sockets, and the brain to see if the cancer has spread.

In most cases the cancer has not spread beyond the eye, and other evaluations are unnecessary. If the cancer appears to have spread beyond the eye, then other assessments such as a blood test, spinal tap (**lumbar puncture**), and/or bone marrow **biopsy** may be recommended. During a spinal tap, a needle is inserted between the vertebrae of the spinal column and a small sample of the fluid surrounding the spinal cord is obtained. In a bone marrow biopsy, a small amount of tissue (bone marrow) is taken from inside the hip or breast bone for examination.

Genetic testing

Establishing whether someone is affected with an inherited or non-inherited form of retinoblastoma can help to ascertain whether other family members such as siblings, cousins, and offspring are at increased risk for developing retinoblastoma. It can also sometimes help guide treatment choices, since patients with an inherited form of retinoblastoma may be at increased risk for developing recurrent tumors or other types of cancers, particularly when treated with radiation. It is helpful for the families of a child diagnosed with retinoblastoma to meet with a genetic specialist such as a genetic counselor and/or geneticist. These specialists can help to ascertain the chances that the retinoblastoma is inherited and facilitate **genetic testing** if desired.

If a patient with unilateral or bilateral retinoblastoma has a relative or relatives with retinoblastoma, it can be assumed that they have an inherited form of retinoblastoma. However, it cannot be assumed that a patient without a family history of the disease has a sporadic form.

Even when there is no family history, most cases of bilateral and trilateral retinoblastoma are inherited, as are most cases of unilateral, multifocal retinoblastoma. However, only 15% of unilateral, unifocal retinoblastoma cases are inherited.

The only way to establish whether someone has an inherited form of retinoblastoma is to see if the retinoblastoma gene is changed or deleted in the blood cells obtained from a blood sample. Approximately 5% to 8% of individuals with retinoblastoma possess a chromosomal abnormality involving the RB1 gene that can be detected by looking at their chromosomes under the microscope. The chromosomes can be seen by obtaining a blood sample. If this type of chromosomal abnormality is detected in a child, then analysis of the parents' chromosomes should be performed. If one of the parents possesses a chromosomal abnormality, then they are at higher risk for having other offspring with retinoblastoma. Chromosome testing would be recommended for the blood relatives of the parent with the abnormality.

Usually, however, a chromosomal abnormality is not detected in a child with retinoblastoma. In this case, specialized DNA tests that look for small RB1 gene changes need to be performed on the blood cells. DNA testing can be difficult, time consuming, and expensive, since there are many possible RB1 gene changes that can cause the gene to become nonfunctional.

If a sample of tumor is available, then it is recommended that DNA testing be performed on the tumor cells prior to DNA testing of the blood cells. This testing can usually identify the gene changes/deletions in the RB1 genes that caused the tumor to develop. In some cases, RB1 gene changes/deletions are not found in the tumor cells (as of 2001, approximately 20% of RB1 gene changes or deletions are not detectable). In these cases, DNA testing of the blood cells will not be able to ascertain whether someone is affected with an inherited or non-inherited form of retinoblastoma.

If the changes in both RB1 genes are detected in the tumor cell, then these same changes can be looked for in the blood cells. If an RB1 gene is deleted or changed in all of the blood cells tested, the patient can be assumed to have been born with a changed/deleted RB1 gene in all of their cells. This person has a 50% chance of passing the RB1 gene change/deletion on to his or her children. Most of the time, this change/deletion has been inherited from a parent. Occasionally the gene change/deletion

occurred spontaneously in the original cell that was formed when the egg and sperm came together at conception (de novo).

If an RB1 gene change/deletion is found in all of the blood cells tested, both parents should undergo blood testing to check for the same RB1 gene change/deletion. If the RB1 gene change/deletion is identified in one of the parents, it can be assumed that the retinoblastoma was inherited and that siblings have a 50% chance of inheriting the altered gene. More distant blood relatives of the parent with the identified RB1 gene change/deletion may also be at risk for developing retinoblastoma. Siblings and other relatives could undergo DNA testing to see if they have inherited the RB1 gene change/deletion.

If the RB1 gene change/deletion is not identified in either parent, then the results can be more difficult to interpret. In this case, there is a 90-94% chance that the retinoblastoma was not inherited.

In some cases, a person with retinoblastoma will have an RB1 gene change/deletion detected in some of their blood cells and not others. It can be assumed that this person did not inherit the retinoblastoma from either parent. Siblings and other relatives would therefore not be at increased risk for developing retinoblastoma. Offspring would be at increased risk since some of the egg or sperm cells could have the changed/deleted RB1 gene. The risks to offspring would probably be less than 50%.

In families where there are multiple family members affected with retinoblastoma, blood samples from multiple family members are often analyzed and compared through DNA testing. Ninety-five percent of the time, this type of analysis is able to detect patterns in the DNA that are associated with a changed RB1 gene in that particular family. When a pattern is detected, at-risk relatives can be tested to establish whether they have inherited an RB1 gene change/deletion.

PRENATAL TESTING If chromosome or DNA testing identifies an RB1 gene/deletion in someone's blood cells, then prenatal testing can be performed on this person's offspring. An amniocentesis or chorionic villus sampling can be used to obtain fetal cells which can be analyzed for the RB1 gene change/deletion or chromosomal abnormality.

Treatment team

If possible, a person with retinoblastoma should be referred to a medical center with a team of cancer specialists. It is important that this team include specialists such as a primary care pediatrician, an ophthalmologist with extensive experience in treating retinoblastoma, pediatric surgeons, radiation oncologists, pediatric medical oncologists, rehabilitation specialists, pediatric nurse specialists, genetic specialists, and social workers.

Clinical staging, treatments, and prognosis

A number of different classification (staging) systems are used to establish the severity of retinoblastoma and aid in choosing an appropriate treatment plan. The most widely used staging system is the Reese-Ellsworth system. This system is used to classify intraocular tumors and predict which tumors are favorable enough that sight can be maintained. The Reese-Ellsworth classification system is divided into:

- Group I (very favorable for maintenance of sight): small solitary or multiple tumors, less than 6.4 mm in size (1 inch = 25.4 mm), located at or below the equator of the eye
- Group II (favorable for maintenance of sight): solitary or multiple tumors, 6.4mm-16mm in size, located at or behind the equator of the eye
- Group III (possible for maintenance of sight): any tumor located in front of the equator of the eye, or a solitary tumor larger than 16 mm in size and located behind the equator of the eye
- Group IV (unfavorable for maintenance of sight): multiple tumors, some larger than 16 mm in size, or any tumor extending in front of the outer rim of the retina (ora serrata)
- Group V (very unfavorable for maintenance of sight): large tumors involving more than half of the retina, or vitreous seeding, in which small pieces of tumor are broken off and floating around the inside of the eye

When choosing a treatment plan, the first important criteria to ascertain is whether the cancer is localized within the eye (intraocular) or has spread to other parts of the body (extraocular). An intraocular retinoblastoma may only involve the retina or could involve other parts of the eye. An extraocular retinoblastoma could involve only the tissues around the eye or could result from the spread of cancer to the brain or other parts of the body.

It is also important to establish whether the cancer is unilateral (one eye) or bilateral (both eyes), multifocal or unifocal. In order for the tumors to be considered multifocal, they must have arisen independently and not as the result of the spread of cancer cells. It is also important to check for trilateral retinoblastoma.

Treatments

The treatment chosen depends on the size and number of tumors, whether the cancer is unilateral or bilateral,

and whether the cancer has spread to other parts of the body. The goal of treatment is to cure the cancer and prevent as much loss of vision as possible. Since the late 1990s, doctors treating patients with retinoblastoma have tended to avoid enucleation and external beam radiation therapy whenever possible, in favor of chemotherapy to reduce the tumor in addition to focal therapies. Improved methods of chemoreduction have led to increasing success in saving patients' eyes, often with some visual function.

TREATMENT OF INTRAOCULAR TUMORS Surgical removal of the affected eye (enucleation) is used when the tumor(s) are so large and extensive that preservation of sight is not possible. This surgery is performed under general anesthetic and usually takes less than an hour. Most children who have undergone this surgery can leave the hospital on the same day. A temporary ball is placed in the eye socket after the surgery. Approximately three weeks after the operation, a plastic artificial eye (prosthesis) that looks like the normal eye is inserted into the eye socket.

Radiation therapy is often used for treatment of large tumors when preservation of sight is possible. External beam radiation therapy involves focusing a beam of radiation on the eye. If the tumor has not spread extensively, the radiation beam can be focused on the cancerous retinal cells. If the cancer is extensive, radiation treatment of the entire eye may be necessary. External beam radiation is performed on an outpatient basis and usually occurs over a period of three to four weeks. Some children may need sedatives prior to the treatment. This type of therapy can result in a temporary loss of a patch of hair on the back of the head and a small area of "sun-burned" skin. Long-term side effects of radiation treatment can include cataracts, vision problems, bleeding from the retina, and decreased growth of the bones on the side of the head. People with an inherited form of retinoblastoma have an increased risk of developing other cancers as a result of this therapy. Some consideration should therefore be given to alternative treatment therapies for those with an inherited form of retinoblastoma.

Photocoagulation therapy is often used in conjunction with radiation therapy but may be used alone to treat small tumors that are located on the back of the eye. Photocoagulation involves using a laser to destroy the cancer cells. This type of treatment is done under local or general anesthesia and is usually not associated with post-procedural pain.

Thermotherapy is also often used in conjunction with radiation therapy or drug therapy (**chemotherapy**). Thermotherapy involves the use of heat to help shrink tumor cells. The heat is either used on the whole eye or localized to the tumor area. It is done under local or general anesthesia and is usually not painful.

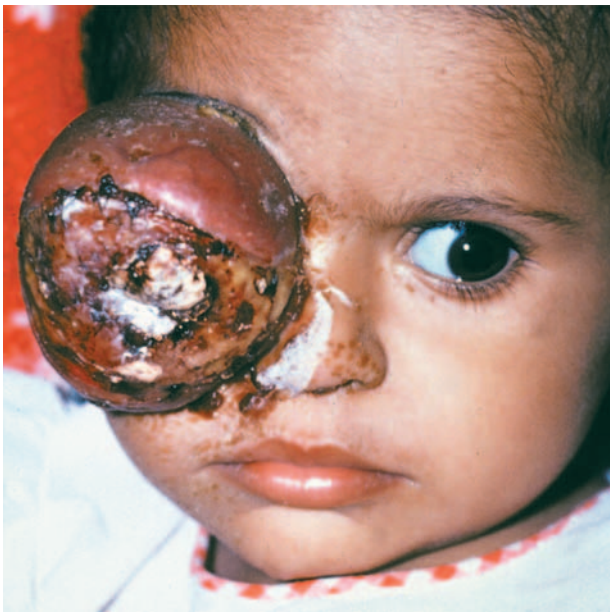
Cryotherapy is a treatment often used in conjunction with radiation therapy but can also be used alone on small tumors located on the front part of the retina. Cryotherapy involves the use of intense cold to destroy cancer cells and can result in harmless, temporary swelling of the external eye and eyelids that can last for up to five days. Eye drops or ointment are sometimes provided to reduce the swelling.

Brachytherapy involves the application of radioactive material to the outer surface of the eye at the base of the tumor. It is generally used for tumors of medium size. A patient undergoing this type of procedure is usually hospitalized for three to seven days. During that time, he or she undergoes one surgery to attach the radioactive material and one surgery to remove it. Eye drops are often administered for three to four weeks following the operation to prevent inflammation and infection. The long-term side effects of this treatment can include cataracts and damage to the retina, which can lead to impaired vision.

Intravenous treatment with one or more drugs (chemotherapy) is often used for treatment of both large and small tumors. Chemotherapy is sometimes used to shrink tumors prior to other treatments such as radiation therapy or brachytherapy. Occasionally, it is also used alone to treat very small tumors.

TREATMENT OF INTRAOCULAR AND UNILATERAL RETINOBLASTOMA Often, by the time that unilateral retinoblastoma is diagnosed, the tumor is so large that useful vision cannot be preserved. In these cases removal of the eye (enucleation) is the treatment of choice. Other therapies are unnecessary if enucleation is used to treat intraocular unilateral retinoblastoma. If the tumor is small enough, other therapies such as external beam radiation therapy, photocoagulation, cryotherapy, thermotherapy, chemotherapy, and brachytherapy may be considered.

TREATMENT OF INTRAOCULAR AND BILATERAL RETINOBLASTOMA If vision can be preserved in both eyes, radiation therapy of both eyes may be recommended. Smaller, more localized tumors can sometimes be treated by local therapies such as cryotherapy, photocoagulation therapy, thermotherapy or brachytherapy. Some centers may use chemotherapy in place of radiation therapy when the tumors are too large to be treated by local therapies or are found over the optic nerve of the eye. Many centers are moving away from radiation treatment and toward chemotherapy because it is less likely to induce future tumors. Enucleation is performed on the more severely affected eye if sight cannot be preserved in both.



This child's right eye is completely covered with a retinoblastoma tumor. *(Custom Medical Stock Photo. Reproduced by permission.)*

EXTRAOCULAR RETINOBLASTOMA There is no proven effective therapy for the treatment of extraocular retinoblastomas. Commonly, radiation treatment of the eyes and chemotherapy is provided.

Prognosis

Individuals with intraocular retinoblastoma who do not have trilateral retinoblastoma usually have a good survival rate with a 90% chance of disease-free survival for five years. Those with extraocular retinoblastoma have less than a 10% chance of disease-free survival for the same amount of time. Trilateral retinoblastoma generally has a very poor prognosis. Patients with trilateral retinoblastoma who receive treatment have an average survival rate of approximately eight months, while those who remain untreated have an average survival rate of approximately one month. Patients with trilateral retinoblastoma who are asymptomatic at the time of diagnosis may have a better prognosis than those who experience symptoms.

Patients with an inherited form of unilateral retinoblastoma have a 70% chance of developing retinoblastoma in the other eye. Retinoblastoma recurs in the other eye in approximately 5% of people with a non-inherited form of retinoblastoma, so it is advisable for even these patients to be closely monitored. People with an inherited form of retinoblastoma who have not undergone radiation treatment have approximately a 26% chance of developing cancer in another part of the body within 50 years of the initial diagnosis. Those with an inherited form who have undergone radiation treatment have a 58% chance of developing a secondary cancer by 50 years after the initial diagnosis. Most of the secondary cancers are skin cancers, bone tumors (osteosarcomas), and soft-tissue **sarcomas**. Soft-tissue sarcomas are malignant tumors of the muscle, nerves, joints, blood vessels, deep skin tissues, or fat. The prognosis for retinoblastoma patients who develop secondary cancers, however, is very poor as of the early 2000s.

Survivors of retinoblastoma are likely to have visual field defects after their cancer treatment is completed, most commonly scotomas, which are areas of lost or depressed vision within an area of normal vision. The size and type of these visual defects are determined by the size and type of the original tumor and the form of therapy used to treat it.

Alternative and complementary therapies

There are no alternative or complementary therapies specific to the treatment of retinoblastoma. Since most people diagnosed with retinoblastoma are small children, most drug-based alternative therapies designed to treat general cancer would not be recommended. Many specialists would, however, stress the importance of establishing a well-balanced diet, including certain fruits, vegetables, and vitamin supplements, to ensure that the body is strengthened in its fight against cancer. Some advocate the use of visualization strategies, in which patients would visualize the immune cells of their body attacking and destroying the cancer cells.

The most common side effects of chemotherapy include nausea and vomiting, and temporary hair loss (alopecia). This treatment can result in a temporary decrease in blood cells, including white blood cells, red blood cells, and platelets.

Coping with cancer treatment

Both retinoblastoma itself and treatments such as enucleation and radiation can result in vision impairment and cause some mild disfigurement around the eye. Children with resulting vision impairment can often be helped by centers and programs for the visually impaired. It is recommended that children who have undergone enucleation should wear protective glasses to protect the remaining eye. Special glasses may be recommended for those who are involved in contact sports. **Reconstructive surgery** following enucleation or radiation treatment may be recommended to improve the cosmetic appearance of the area around the eye. Eye drops and ointments may also be used to counteract side effects such as swelling and inflammation that can be associated with cancer treatments such as brachytherapy and cryotherapy.

KEY TERMS

Amniocentesis—Prenatal testing performed at 16 to 20 weeks of pregnancy that involves inserting a needle through the abdomen of a pregnant mother and obtaining a small sample of fluid from the amniotic sack, which contains the fetus. Often is used to obtain a sample of the fetus' cells for biochemical or DNA testing.

Benign tumor—An abnormal proliferation of cells that does not spread to other parts of the body.

Bilateral—Affecting both eyes.

Brachytherapy—Cancer treatment that involves the application of radioactive material to the site of the tumor.

Cryotherapy—Cancer treatment in which the tumor is destroyed by exposure to intense cold.

Chromosome—A microscopic structure found within each cell of the body, made of a complex of proteins and DNA.

Chorionic villus sampling (CVS)—Prenatal testing performed at 10 to 12 weeks of pregnancy, which involves inserting a catheter through the vagina of a pregnant mother or inserting a needle through the abdomen of the mother and obtaining a sample of placenta. Often is used to obtain a sample of the fetus' cells for biochemical or DNA testing.

DNA (deoxyribonucleic acid)—The hereditary material that makes up genes; influences the development and functioning of the body.

DNA testing—Testing for a change or changes in a gene or genes.

Enucleation—Surgical removal of the eye.

Equator—Imaginary line encircling the eyeball and dividing the eye into a front and back half.

Extraocular retinoblastoma—Cancer that has spread from the eye to other parts of the body.

Gene—A building block of inheritance, made up of a compound called DNA (deoxyribonucleic acid) and containing the instructions for the production of a particular protein. Each gene is found in a specific location on a chromosome.

Intraocular retinoblastoma—Cancer that is limited to the eye and has not spread to other parts of the body.

Malignant tumor—An abnormal proliferation of cells that can spread to other sites.

Multifocal—More than one tumor present.

Ophthalmologist—Physician specializing in the diseases of the eye.

Optic nerve—The part of the eye which contains nerve fibers that transmit signals from the eye to the brain.

Oncologist—A physician specializing in the diagnosis and treatment of cancer

Photocoagulation—Cancer treatment in which the tumor is destroyed by an intense beam of laser light.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

Protein—A substance produced by a gene that is involved in creating the traits of the human body, such as hair and eye color, or is involved in controlling the basic functions of the human body, such as control of the cell cycle.

Retina—The light-sensitive layer of the eye that receives images and sends them to the brain.

Scotoma—An area of lost or depressed vision within the visual field surrounded by an area of normal vision. Survivors of retinoblastoma frequently develop scotomas.

Somatic cells—All the cells of the body with the exception of the egg and sperm cells.

Tumor—A growth of tissue resulting from the uncontrolled proliferation of cells.

Tumor-suppressor gene—Gene involved in controlling normal cell growth and preventing cancer.

Unifocal—Only one tumor present in one eye.

Unilateral—Affecting only one eye.

Vitreous—The transparent gel that fills the back part of the eye.

Vitreous seeding—When small pieces of tumor have broken off and are floating around the vitreous.

If chemotherapy is used, the child may experience side effects such as nausea, vomiting, and hair loss. The patient may also experience a decreased level of: white blood cells, which can cause an increased susceptibility to infection; red blood cells, which can result in **fatigue** or shortness of breath; and platelets, which can cause an increased risk of bruising or prolonged bleeding after an injury. These symptoms are generally temporary and can often be treated. There are a number of drugs on the market that can decrease or

QUESTIONS TO ASK THE DOCTOR

- What form and stage of retinoblastoma does my child have? Has the cancer spread beyond the eye?
- Was this an inherited disease? Should other family members be tested?
- What are the chances of maintaining my child's sight? What treatment options are appropriate for this?
- Are there support groups in the area to help my family cope with this diagnosis?

even eliminate **nausea and vomiting**. Early recognition of infections and treatments with **antibiotics** are very important. All high fevers should be reported to a physician immediately, and may require hospitalization. Platelet transfusions are sometimes necessary for the replacement of platelets. Loss of hair can be very traumatic to an older child, but the use of a wig until the hair grows back may be helpful.

Clinical trials

As of 2004 the National Cancer Institute is conducting four clinical trials for the treatment of retinoblastoma and one intensive study of individuals and families at high risk for cancer. The treatment trials include two forms of combination chemotherapy; the use of arsenic trioxide; and combination chemotherapy followed by bone marrow transplantation.

Prevention

Although retinoblastoma cannot be prevented, appropriate screening and surveillance should be applied to all at-risk individuals to ensure that the tumor(s) are diagnosed at an early stage. The earlier the diagnosis, the more likely that an eye can be salvaged and vision maintained.

Screening of people diagnosed with retinoblastoma

Children who have been diagnosed with retinoblastoma should receive periodic dilated retinal examinations until the age of five. Young children will need to undergo these evaluations under anesthetic. After five years of age, periodic eye examinations are recommended. It may be advisable for patients with bilateral retinoblastoma or an inherited form of retinoblastoma to undergo periodic screening for the brain tumors found in trilateral retinoblastoma. There are no specific screening protocols designed to detect non-ocular tumors. All lumps and complaints of **bone pain**, however, should be thoroughly evaluated.

Screening of relatives

When a child is diagnosed with retinoblastoma, it is recommended that parents and siblings receive a dilated retinal examination by an ophthalmologist who is experienced in the diagnosis and treatment of the disease. It is also recommended that siblings continue to undergo periodic retinal examinations under anesthetic until they are three years of age. From three to seven years of age, periodic eye examinations are recommended. The retinal examinations can be avoided if DNA testing indicates that the patient has a non-inherited form of retinoblastoma or if the sibling has not inherited the RB1 gene change/deletion. Any relatives who are found through DNA testing to have inherited an RB1 gene change/deletion should undergo the same surveillance procedures as siblings.

The children of someone diagnosed with retinoblastoma should also undergo periodic retinal examinations under anesthetic. Retinal surveillance should be performed unless DNA testing proves that their child does not possess the RB1 gene change/deletion. If desired, prenatal detection of tumors using ultrasound may also be performed. During the ultrasound procedure, a handheld instrument is placed on the maternal abdomen or inserted vaginally. The ultrasound produces sound waves that are reflected back from the body structures of the fetus, producing a picture that can be seen on a video screen. If a tumor is detected through this evaluation, the affected baby may be delivered a couple of weeks earlier. This can allow for earlier intervention and treatment.

Special concerns

Since retinoblastoma most often affects children, parents have the difficult task of helping the doctor explain the condition and prognosis to their child. It is very important for parents to be open and honest about the disease, and some have found it helpful to read their child a story about another child who has faced the same condition.

Dealing with a diagnosis of retinoblastoma can be very stressful and frightening for children. Talking to other children with the same diagnosis can be helpful. Talking to a counselor or using relaxation therapies may also help a child deal with the emotions and fear associated with retinoblastoma.

Children with retinoblastoma may experience difficulties with their self image because of the temporary loss of hair or the loss of one or both eyes. It is important to remind these children of their many positive qualities. It is also important to teach children strategies for coping

with others who may tease them or ask them questions about their condition.

The diagnosis of retinoblastoma can greatly impact the whole family. For some, therapy may be necessary to ensure that the family can cope with the stresses associated with this diagnosis. Talking with other families who have children with retinoblastoma can also be of help.

In general, most children and families cope very well with the diagnosis of retinoblastoma. Since the prognosis is usually very good, it is important that parents strive to maintain a positive outlook.

Resources

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ORGANIZATIONS

American Academy of Ophthalmology (AAO). P. O. Box 7424, San Francisco, CA 94120-7424. (415) 561-8500. Fax: (415) 561-8533. <http://www.aao.org>.

Institute for Families with Blind Children. PO Box 54700, Mail Stop 111, Los Angeles, CA 90054-0700. (213) 669-4649.

National Retinoblastoma Parents Group. PO Box 317, Watertown, MA 02471 (800) 562-6265. Fax: (617) 972-7444. napvi@perkins.pvt.k12.ma.us.

Retinoblastoma International. 4650 Sunset Blvd., Mail Stop #88, Los Angeles, CA 90027. (323) 669-2299. info@retinoblastoma.net. <http://www.retinoblastoma.net/rbi/index_rbi.htm>.

The Retinoblastoma Society. Saint Bartholomew's Hospital, London, UK EC1A 7BE. Phone: 020 7600 3309 Fax: 020 7600 8579. <http://ds.dial.pipex.com/rbinfo>.

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Rhabdomyosarcoma

Definition

Rhabdomyosarcoma is a childhood cancer. It begins in cells that will become skeletal muscle cells. Skeletal muscle is attached to bones and is different from the smooth muscle that lines the intestinal tract (esophagus, stomach, small and large intestines). With rhabdomyosarcoma, these muscle cells grow uncontrollably and form masses or lumps called tumors. They can start almost anywhere in the body where there is skeletal muscle.

Description

Rhabdomyosarcomas can start in any organ that contains skeletal muscle cells, but most commonly tumors are found in the head and neck and in the prostate, bladder, and vagina. From 5–8% of all cancers diagnosed in children are rhabdomyosarcomas.

Demographics

Rhabdomyosarcoma occurs most frequently in children ages 2 to 6 and 15 to 19 years old. More males than females develop rhabdomyosarcomas. Among younger children, the tumor is usually in the head and neck and may involve the area surrounding the eye. Less often, young children develop rhabdomyosarcomas of the genitourinary tract (bladder, prostate, vagina).

In the older age group, the most likely site is the male genitourinary tract, especially the testes and surrounding area. Other body parts where rhabdomyosarcoma may begin are on the arms, legs, trunk, or deep inside the abdomen (retroperitoneum).

Some cases of rhabdomyosarcoma run in families and are linked to genetic syndromes. Immediate family members of children with rhabdomyosarcoma are at increased risk of developing certain cancers that are not rhabdomyosarcomas, such as breast and brain tumors.

Causes and symptoms

The causes of rhabdomyosarcoma are not known. Certain inherited conditions that run in families increase the risk of developing this cancer. Rhabdomyosarcoma has been linked to medical conditions such as fetal alcohol syndrome, neurofibromatosis, Gorlin's syndrome, and **Li-Fraumeni syndrome**.

The symptoms of rhabdomyosarcoma depend on the site of the tumor and whether it has spread. When rhabdomyosarcoma begins in the head, it may involve the area surrounding the eye, the nasal passages or the ear and throat. Tumors in these areas may cause swelling, especially around the eye; blocked nasal passages or sinuses; ear pain and bleeding; and difficulties swallowing. Rhabdomyosarcomas in the head and neck may also put pressure on the brain or nerves.

When rhabdomyosarcoma affects an arm, leg or other body part, the swelling may be mistaken for a bruise or other injury. When the genitals or urinary tract are involved, there may be symptoms such as recurring urinary tract infections, blood in the urine, **incontinence**, or blockage of the urinary tract or rectum.

Rhabdomyosarcoma affecting the testes may cause swelling of the scrotum. When the uterus or vagina is affected, there may be a mass or small tumor pushing into the vaginal canal.

Diagnosis

Some patients who have rhabdomyosarcomas go to the doctor because they have discovered a lump or mass or swelling on a body part. Others have symptoms related to the part of the body that is affected by the tumor. The patient's doctor will take a detailed medical history to find out about the symptoms. The history is followed by a complete physical examination with special attention to the suspicious symptom or body part.

Depending on the location of the tumor (mass or lump), the doctor will order **imaging studies** such as **x ray**, ultrasound, **computed tomography** (CT) scans and **magnetic resonance imaging** (MRI) to help determine the size, shape and exact location of the tumor. The doctor may also order bone scans to determine if the tumor has spread to bones. Blood tests will be done and an examination of the bone marrow also may be performed.

A **biopsy** of the tumor is necessary to make the diagnosis of rhabdomyosarcoma. During a biopsy, some tissue from the tumor is removed. The tissue sample is examined by a pathologist, a doctor who specializes in the study of diseased tissue.

Types of biopsy

The type of biopsy done depends on the location of the tumor. For some small tumors, such as those on the arm or leg, the doctor may perform an excisional biopsy, removing the entire tumor and a margin of surrounding normal tissue. Most often, the doctor will perform an incisional biopsy, a procedure that involves cutting out only a piece of the tumor. This biopsy provides a core of tissue from the tumor that is used to determine its type and grade.

Treatment team

Patients with rhabdomyosarcoma are usually cared for by a multidisciplinary team of health professionals. The patient's pediatrician, or primary care doctor may refer the patient to other physician specialists, such as surgeons and oncologists (doctors who specialize in cancer medicine). Radiologic technicians perform x ray, CT and MRI scans and nurses and laboratory technicians may obtain samples of blood, urine and other laboratory tests.

Before and after any surgical procedures, specially trained nurses may explain the procedures and help to prepare patients and families. Depending on the tumor location and treatment plan, patients may also benefit from rehabilitation therapy with physical therapists and nutritional counseling from dieticians.

Clinical staging, treatments, and prognosis

Staging

The purpose of staging a tumor is to determine how far it has advanced. This is important because treatment varies depending on the stage. Stage is determined by the size of the

tumor, whether the tumor has spread to nearby lymph nodes,and whether the tumor has spread elsewhere in the body.

Tumors are staged using numbers to designate Stages I through IV. The higher the number, the more the tumor has advanced. Stage I rhabdomyosarcomas have not extended beyond the site where they began; they are limited to a single muscle or organ. Stage II tumors show signs of spread beyond the muscle or organ where they began. Stage III rhabdomyosarcomas are tumors that could not be removed in their entirety by surgery. As a result, some tumor remains at the site where it began. Stage IV rhabdomyosarcomas have involved either lymph nodes or have spread to distant parts of the body.

Treatment

Treatment for rhabdomyosarcoma varies depending on the location of the tumor, its size and grade, and the extent of its spread. By the time most cases of rhabdomyosarcoma are diagnosed, there has already been some spread of the disease. For these patients, the goals of treatment are to remove or control the tumor and combat the spread of the cancer.

Generally, when completely removing the tumor will not sharply reduce function, rhabdomyosarcoma tumors are surgically removed. The site, size, and extent of the tumor determine the type of surgery performed. The goal of removing as much tumor as possible is to reduce the amount of radiation needed after surgery. The part of the body where the tumor was removed is treated with radiation to destroy remaining tumor cells. Many patients also receive **chemotherapy**.

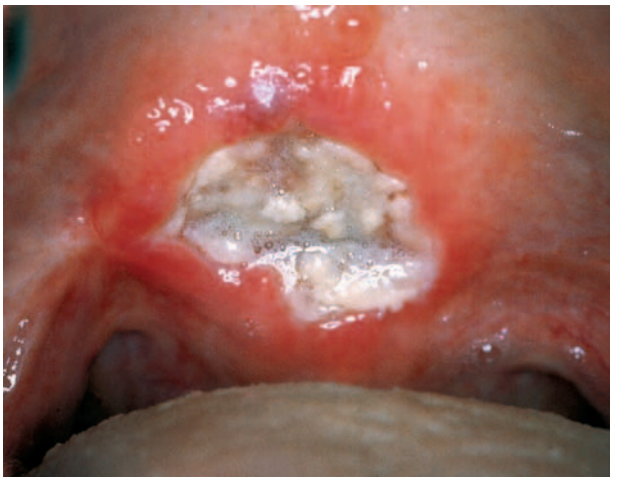
When the disease has spread throughout the body, there may be no benefit from surgical removal of the tumor. These cases, usually patients with Group IV tumors, are treated with chemotherapy.

Side effects

The surgical treatment of rhabdomyosarcoma carries risks related to the surgical site, such as loss of function resulting from head and neck surgeries. Head and neck surgeries also may result in deformities that may be cosmetically unsatisfactory. There also are the medical risks associated with any surgical procedure, such as reactions to general anesthesia or infection after surgery.

The side effects of **radiation therapy** depend on the site being radiated. Radiation therapy can produce side effects such as **fatigue**, skin rashes, nausea, **diarrhea**, and secondary cancers. Most of the side effects lessen or disappear completely after the radiation therapy has been completed.

The side effects of chemotherapy vary depending on the medication, or combination of anticancer drugs, used.



Rhabdomyosarcoma, a malignant tumor affecting the inside of the mouth. *(Copyright Eamonn McNulty, Science Source/ Photo Researchers, Inc. Reproduced by permission.)*

Nausea, vomiting, **anemia**, lower resistance to infection and hair loss are common side effects. Medication may be given to reduce the unpleasant side effects of chemotherapy.

Alternative and complementary therapies

Many patients explore alternative and complementary therapies to help to reduce the stress associated with illness, improve immune function and feel better. While there is no evidence that these therapies specifically combat disease, activities such as biofeedback, relaxation, therapeutic touch, massage therapy and guided imagery have been reported to enhance well-being.

Prognosis

The outlook for patients with rhabdomyosarcoma varies. It depends on the site of the tumor, how the cancer cells look under the microscope, and extent of spread. For example, patients with tumors affecting the area around the eye and the bladder are more likely to do well than patients with tumors that begin deep within the chest or abdomen.

Rhabdomyosarcoma may spread to areas near the tumor and it can spread to nearby lymph glands. To spread to distant parts of the body, the cells travel in the blood or through the lymph glands. The most common sites for **metastasis** (spread) are the lymph glands near the tumor, the lung, liver, bone marrow, and brain. In general, tumors that have spread widely throughout the body are not associated with favorable survival rates.

Patients with Stage I tumors that are completely removed surgically have excellent prognoses; eight-year survival is nearly 75%. Sixty five percent of patients with

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of cancerous cells or by killing them.

Metastasize—The spread of cancer cells from a primary site to distant parts of the body.

Oncologist—A doctor who specializes in cancer medicine.

Pathologist—A doctor who specializes in the diagnosis of disease by studying cells and tissues under a microscope.

Radiation therapy—Treatment using high energy radiation from X-ray machines, cobalt, radium, or other sources.

Stage—A term used to describe the size and extent of spread of cancer.

QUESTIONS TO ASK THE DOCTOR

- What stage is the rhabdomyosarcoma?
- What are the recommended treatments?
- What are the side effects of the recommended treatment?
- Is treatment expected to cure the disease or only to prolong life?

Stage II tumors are disease free after 8 years. Stage I and II rhabdomyosarcomas account for about 40% of all cases.

About 40% of patients with Stage III and 15% of those with Stage IV rhabdomyosarcomas are disease free after 8 years. Patients with tumors that do not respond to treatment and those who suffer recurrences have poor outlooks for long-term survival.

Coping with cancer treatment

Toddlers, children and teens undergoing cancer treatment have special needs. The diagnosis of a life-threatening illness, surgery and radiation or chemotherapy may cause fear, anxiety, **depression** and loss of self-esteem. Toddlers may be especially fearful when they are separated from their parents for medical tests and hospital stays. Disruption of their normal routines and discomfort from diagnostic tests and treatment may also cause anxiety. Older children face additional social problems including making up missed school work, explaining the illness and treatment to friends, and coping with physical limitations or disability.

Teens with serious illnesses and disabilities face special conflicts and challenges. One conflict is between the teen's growing desire for independence and the reality of dependence on others for the activities of daily living. It is important for teens to be fully informed about their disease and treatment plan and involved in treatment decision making. Many teens benefit from continuing contact with friends, classmates, teachers, and family during hospital stays and recovery at home.

Depression, emotional distress, and anxiety associated with the disease and its treatment may respond to counseling from a mental health professional. Play therapy often helps toddlers and young children to reveal and express their feelings about illness and treatment. Many cancer patients and their families find participation in mutual aid and group support programs help to relieve feelings of isolation and loneliness. By sharing problems with others who have lived through similar difficulties patients and families can exchange ideas and coping strategies.

Clinical trials

About 30 clinical studies were underway during 2001. For example, in one clinical trial at John Hopkins Oncology Center, patients with recurring or widespread rhabdomyosarcoma were being treated with chemotherapy to stop tumor cells from dividing and simultaneously being given stem cells (bone marrow transplantation) to replace the immune cells killed by chemotherapy.

Other **clinical trials** compare different combinations of chemotherapy drugs to find out which combination is most effective. For example, in one study, patients with previously untreated rhabdomyosarcoma were randomly assigned to two different combinations of chemotherapy drugs. Along with radiation therapy, patients in one group received three drugs, **vincristine**, **dactinomycin**, and **cyclophosphamide** once a week. Patients in the other group were given vincristine, cyclophosphamide, and topotecan, instead of dactinomycin.

Other types of clinical research study individuals and families at high risk of cancer to help identify cancer genes. To learn more about clinical trials visit the National Cancer Institute (NCI) CancerNet web site at http://cancernet.nci.nih.gov/ or the Pediatric Oncology Branch of the National Cancer Institute web site at <http://www.dcs.nci.nih.gov/pedonc>.

Prevention

Since the causes of rhabdomyosarcoma are not known, there are no recommendations about how to prevent its development. Among families with an inherited tendency to develop soft tissue **sarcomas**, careful monitoring may help to ensure early diagnosis and treatment of the disease.

Special concerns

Rhabdomyosarcoma, like other cancer diagnoses, may produce a range of emotional reactions in patients and families. Education, counseling and participation in group support programs can help to reduce feelings of guilt, fear, anxiety and hopelessness. For many parents suffering from spiritual distress, visits with clergy members and participation in organized prayer may offer comfort.

Resources

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PERIODICALS

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Road, N.E., Atlanta, GA 30329. (800)227–2345.

Cancer Research Institute. 681 Fifth Avenue, New York, NY 10022. (800)992–2623.

National Cancer Institute Clinical Cancer Trials. <http://cancertrials.nci.nih.gov.>.

National Cancer Institute (National Institutes of Health). 9000 Rockville Pike, Bethesda, MD 20892. (800)422–6237.

The Pediatric Oncology Branch of the National Cancer Institute. (877) 624–4878 or (301)496–4256. <http://www.dcs.nci.nih.gov/pedonc/Index.html>.

Barbara Wexler, M.P.H.

Richter's syndrome

Definition

Richter's syndrome is a rare and aggressive type of acute adult leukemia that results from a transformation of **chronic lymphocytic leukemia** into diffuse large cell **lymphoma**.

Description

Leukemia is a group of cancers of the white blood cells. In adults, white blood cells are made in the bone marrow of the flat bones (skull, shoulder blades, ribs, hip bones). There are three main types of white blood cells: granulocytes, monocytes, and lymphocytes. Richter's syndrome concerns only the lymphocytes.

Lymphocytic leukemia develops from lymphocytes in the bone marrow. Unlike many other cancers in which a tumor starts growing in one particular location, lymphocytic leukemia is a disease of blood cells that travel throughout the body. In chronic (long-term) lymphocytic leukemia (CLL), lymphocytes do not follow a normal life cycle, and eventually, too many will exist in the blood. They are abnormal and do not fight infections well.

In a small percentage of people, CLL, even when it is treated, transforms into a new kind of aggressive blood cancer called diffuse large cell lymphoma. When this transformation occurs, it is called Richter's syndrome. The disease is named for the American pathologist Maurice Nathaniel Richter, who practiced medicine early in the twentieth century.

Demographics

Richter's syndrome is a disease of older adults. It is an extremely rare disease. The American Cancer Society estimates that in 2000, there were 8,100 new cases of chronic lymphocytic leukemia, and that 98% of these were in adults. Of these 8,100 new cases, only a handful will develop into Richter's syndrome. In general, people who are more likely to get CLL are those who smoke, have been exposed to high doses of radiation, or who have had long-term exposure to herbicides and pesticides. People who have close relatives (parent, siblings or children) with CLL are also more likely to develop the disease. However, none of these risk factors predict whether CLL will develop into Richter's syndrome.

Causes and symptoms

Scientists have yet to understand why some people develop Richter's syndrome and others do not. So far, no firm genetic or environmental links have been found.

When the transformation from CLL to Richter's syndrome occurs, a change occurs in the way the lymphocytes look under the microscope. In addition, lymph nodes swell, tumors grow rapidly in the lymph system, and the patient may experience **fever**, **night sweats**, and **weight loss**. The patient's health deteriorates rapidly and severely.

KEY TERMS

Lymph nodes—Small, bean-shaped collections of tissue found in lymph vessels. They produce cells and proteins that fight infection and filter lymph. Nodes are sometimes called lymph glands.

Lymph system—Primary defense against infection in the body. The tissues, organs, and channels (similar to veins) that produce, store, and transport lymph and white blood cells to fight infection.

Lymphoma—A cancer of the lymph system.

QUESTIONS TO ASK THE DOCTOR

- What kind of changes in my body can I expect to see from this cancer?
- What is the treatment plan?
- What are the likely side effects of the treatment plan?
- How long am I likely to survive?
- Since Richter's syndrome is rare, how much experience do you have with this disease?
- Are there hospitals that specialize in the treatment of Richter's syndrome where I might receive treatment unavailable here?

Diagnosis

Diagnosis is made by examining blood cells under microscope and by a bone marrow **biopsy**. This is the same test used to diagnose CLL. A small amount of bone marrow from one of the flat bones is drawn out with a needle for laboratory examination. In some cases, lymph nodes are also removed and examined in the laboratory.

Treatment team

Since a person who develops Richter's syndrome is already a cancer patient, a treatment team is already in place. This team usually includes an oncologist (cancer specialist), a hematologist (blood specialist) and possibly a radiation oncologist (specialist in **radiation therapy**), radiation or **chemotherapy** technicians, and nurses with special training in cancer care. With the development of Richter's syndrome, a social worker or counselor may be added to the team.

Clinical staging, treatments, and prognosis

Richter's syndrome is not staged. Chemotherapy is used to treat Richter's syndrome, although treatments are often unsuccessful. In addition, allogenic **bone marrow transplantation** is currently being tried in some patients. This treatment is not common and is not done at many cancer centers. For Richter's syndrome, the median survival rate (the time to which half the patients survive) is less than one year.

Alternative and complementary therapies

Alternative and complementary therapies range from herbal remedies, vitamin supplements, and special diets to spiritual practices, acupuncture, massage, and similar treatments. When these therapies are used in addition to conventional medicine, they are called complementary therapies. When they are used instead of conventional medicine, they are called alternative therapies.

There are no specific alternative therapies directed toward Richter's syndrome. However, good nutrition and activities that reduce stress and promote a positive view of life have no unwanted side effects and may help improve the quality of life.

Unlike traditional pharmaceuticals, complementary and alternative therapies are not evaluated by the United States Food and Drug Administration (FDA) for either safety or effectiveness. Patients should be wary of "miracle cures." In order to avoid any harmful side effects or interference with regular cancer treatment, patients should notify their doctors if they are using any herbal remedies, vitamin supplements, or other unprescribed treatments. Alternative and experimental treatments normally are not covered by insurance.

Coping with cancer treatment

Richter's syndrome is usually fatal within a short time. Coming to grips with this is tremendously stressful for both the patient and family members. In addition, chemotherapy treatments can cause **fatigue**, nausea, vomiting, and other uncomfortable side effects. Some patients decide to end treatment rather than undergo this discomfort when their chance of recovery is almost nonexistent. Others wish to continue full treatment.

This and many other personal decisions are issues to discuss with loved ones. It is often helpful for loved ones to have the support of a therapist, religious leader, or other counselor at this time when emotions are intense and often conflicting. Hospice staff members or hospital social workers or chaplains can direct patients and family members to resources that address their individual needs.

Clinical trials

As of 2001, many ongoing **clinical trials** related to chronic lymphocytic lymphoma may be appropriate for people with Richter's syndrome. Participation is always voluntary. The selection of clinical trials underway changes frequently. Current information on what clinical trials are available and where they are being held is available by entering the search term "chronic lymphocytic lymphoma" at the following web sites:

- National Cancer Institute. <http://cancertrials.nci.nih.gov> or (800) 4-CANCER.
- National Institutes of Health Clinical Trials. <http://clinicaltrials.gov>.
- Center Watch: A Clinical Trials Listing. <http://www.centerwatch.com>.

Prevention

There is no known way to prevent the transformation of CLL into Richter's syndrome.

Resources

PERIODICALS

Rodriguez, J., et al. "Allogenic Haematopoietic Transplantation for Richter's Syndrome." *British Journal of Haematology*. 110 (April 2000): 897–9.

ORGANIZATIONS

American Cancer Society. National Headquarters, 1599 Clifton Rd. NE, Atlanta, GA 30329. 800(ACS)-2345). <http://www.cancer.org>.

Cancer Information Service, National Cancer Institute. Building 31, Room 10A19, 9000 Rockville Pike, Bethesda, MD 20892. (800) 4-CANCER. <http://www.nci.nih.gov/cancerinfo/index.html>.

Leukemia & Lymphoma Society. 1311 Mamaroneck Ave., 3rd floor, White Plains, NY 10605. (800) 955-4572. <http://www.leukemia-lymphoma.org>.

National Leukemia Research Association, Inc. 585 Stewart Ave., Suite 536, Garden City, NY 11530. (516) 222-1944.

Tish Davidson, A.M.

Rituximab

Definition

Rituximab is a humanized monoclonal antibody that selectively binds to CD20, a protein found on the surface of normal and malignant B cells and is used to reduce the numbers of circulating B cells in patients who have B-cell non-Hodgkin's **lymphoma** (NHL). Rituximab is sold as Rituxan in the United States.

Purpose

Rituximab is a monoclonal antibody used to treat NHL characterized by overgrowth of B cells, the cell involved in about 85% of NHL malignancies. Of all the B-cell cancers more than 90% express the CD20 protein on the cell surface, a requirement for the proper function of rituximab. By binding the CD20 protein on the B cell, the antibody targets it for removal from the circulation. Based on data gathered in the laboratory developers believe that rituximab triggers both cell-mediated and complement-mediated means to kill the B cells, two different methods that the immune system uses to eliminate foreign cells. Binding of the antibody may also trigger apoptosis, or programmed cell death, of the B cells.

Rituximab has been most effective against low-grade (indolent) or follicular B-cell NHL. Low-grade (slow progression) NHL often responds well to initial treatment, but frequently relapses, making rituximab a welcome addition to the treatment options. Additionally, rituximab has been used for a second course of treatments after relapse with some success. As most patients with NHL are in stage III or IV by the time of diagnosis and treatment, experience with rituximab treatment are primarily with those stages of the disease.

As of spring 2001 **clinical trials** were being held testing the ability of this drug to work against several other types of cancers, including newly diagnosed NHL, intermediate- or high-grade (aggressive) NHL, AIDS-associated NHL, **Waldenström's macroglobulinemia**, **Hodgkin's disease**, **hairy cell leukemia** (HCL), **chronic lymphocytic leukemia** (CLL), **multiple myeloma**, **mantle cell lymphoma**, and large cell lymphoma.

Description

Rituximab is produced in the laboratory using genetically engineered single clones of B cells. Like all antibodies it is a Y-shaped molecule that can bind to one particular substance, the antigen for that monoclonal antibody. For rituximab that antigen is CD20, a protein found on the surface of B cells. Rituximab is a humanized antibody, meaning that the regions that bind CD20, located on the tips of the Y branches, are derived from mouse antibodies but the rest of the antibody is human sequence. The presence of the human sequences helps to reduce the **immune response** by the patient against the antibody itself—a problem seen when complete mouse antibodies were used for cancer therapies. The human

KEY TERMS

Antibody—A protective protein made by the immune system in response to an antigen, also called an immunoglobulin.

Apoptosis—Internal system for cell death, also called programmed cell death.

CD20—A protein found on the surface of normal and malignant B cells.

Humanization—Fusing the constant and variable framework region of one or more human immunoglobulins with the binding region of an animal immunoglobulin, done to reduce human reaction against the fusion antibody.

Monoclonal—Genetically engineered antibodies specific for one antigen.

sequences also help to ensure that the various cell-destroying mechanisms of the human immune system are properly triggered with binding of the antibody.

In 1997 Rituximab was the first unconjugated (not linked to a radioactive isotope or toxin) antibody approved for use by the FDA to treat cancer. It is specifically approved for treatment of low-grade or follicular B-cell NHL. Administration of the antibody resulted in either complete or partial responses in a little less than half of those patients.

Rituximab can be used alone or in combination with other chemotherapeutic drugs. Specifically, very good results have been seen when used in combination with the CHOP **chemotherapy** regimen (**cyclophosphamide**, **doxorubicin**, **vincristine**, and prednisone). When used in combination, dosages of the antibody given before beginning chemotherapy, alternating with the other drugs, then after the chemotherapy as a "mop-up" have proven effective.

There are a number of clinical trials in progress testing the ability of rituximab to work in combination with other chemotherapy drugs, treatments, and cytokines. Some substances and treatments being tested include interleukins 2 and 11, stem cell transplantation, radioimmunotherapy, vaccination, and a wide variety of other chemotherapy combinations.

Recommended dosage

The recommended dosage for patients with low-grade or follicular NHL is 375 mg/m2 infused intravenously. The infusion is given at weekly intervals for four total dosages. Acetominophen and **diphenhydramine** hydrochoride are given 30-60 minutes before the infusion to help reduce side effects. If given as a retreatment the dosage is the same. Clinical trials were ongoing in 2001 to help clarify the ideal dosage and treatment schedule for this drug. Generally, decrease in symptoms occurs at an average of 55 days after the last administration of the antibody.

Precautions

Serious (even fatal) infusion reactions, especially with the first infusion, have been known with this drug. There are a number of patient conditions that can make taking this drug more dangerous. Specifically, heart problems such as arrhythmias and high blood pressure, and the medications taken to treat those conditions, can be a problem with this treatment.

Side effects

The majority of side effects occur after or during the first infusion of the drug. Some common side effects include dizziness, feeling of swelling of tongue or throat, **fever** and chills, flushing of face, headache, **itching**, nausea and vomiting, runny nose, shortness of breath, skin rash, and unusual fatigue.

Less common side effects include black, tarry stools; blood in urine or stools; fever or chills with cough or hoarseness; lower back or side pain, or painful or difficult urination; pain at place of injection; pinpoint red spots on skin; red, itchy lining of eye; swelling of feet or lower legs; unusual bleeding or bruising; and unusual weakness.

Although they are very rare this drug does have serious side effects such as chest pain and irregular heartbeat, particularly in patients already having heart conditions. It can also cause serious effects on the blood cells such as low red blood cell count (**anemia**) and low white blood cell count (**neutropenia**). Additionally, this drug has caused low blood pressure (hypotension).

In patients with high tumor burden (a large number of circulating malignant B cells) this drug can cause a side effect called **tumor lysis syndrome**. Thought to be due to the release of the lysed cells' contents into the blood stream, it can cause a misbalance of urea, uric acid, phosphate, and calcium in the urine and blood. Patients at risk for this side effect must keep hydrated and can be given **allopurinol** (an anitgout medication) before infusion.

Interactions

There have been no formal drug interaction studies done with rituximab.

Rofecoxib *see* **Cyclooxygenase 2 inhibitors**

S

Salivary gland tumors

Definition

A salivary gland tumor is an uncontrolled growth of cells that originates in one of the many saliva-producing glands in the mouth.

Description

The tongue, cheeks, and palate (the hard and soft areas at the roof of the mouth) contain many glands that produce saliva. In saliva there are enzymes, or catalysts, that begin the breakdown (digestion) of food while it is still in the mouth. The glands are called salivary glands because of their function.

There are three big pairs of salivary glands in addition to many smaller ones. The parotid glands, submandibular glands and sublingual glands are the large, paired salivary glands. The parotids are located inside the cheeks, one below each ear. The submandibular glands are located on the floor of the mouth, with one on the inner side of each part of the lower jaw, or mandible. The sublingual glands are also in the floor of the mouth, but they are under the tongue.

The parotids are the salivary glands most often affected by tumors. Yet most of the tumors that grow in the parotid glands are benign, or not cancerous. Approximately 8 out of 10 salivary tumors diagnosed are in a parotid gland. One in 10 diagnosed is in a submandibular gland. The remaining 10% are diagnosed in other salivary glands.

In general, glands more likely to show tumor growth are also glands least likely to show malignant tumor growth. Thus, although tumors of the sublingual glands are rare, almost all of them are malignant. In contrast, about one in four tumors of the parotid glands is malignant.

Cancers of the salivary glands begin to grow in epithelial cells, or the flat cells that cover body surfaces. Thus, they are called carcinomas.

Demographics

Cancers in the mouth account for fewer than 2% of all cases of cancer and about 1.5% of cancer deaths. About 7% of all cancers diagnosed in the head and neck region are diagnosed in a salivary gland. Men and women are at equal risk.

Mortality from salivary gland tumors in the United States is higher among male African Americans below the age of 50 than among older workers of any race or either sex. The reasons for these findings are not clear as of early 2004.

Causes and symptoms

When survivors of the 1945 atomic bombings of Nagasaki and Hiroshima began to develop salivary gland tumors at a high rate, radiation was suspected as a cause. Ionizing radiation, particularly gamma radiation, is a factor that contributes to tumor development. So is **radiation therapy**. Adults who received radiation therapy for enlarged adenoids or tonsils when they were children are at greater risk for salivary gland tumors.

Another reported risk factor is an association between wood dust inhalation and adenocarcinoma of the minor salivary glands of the nose and paranasal sinuses. There is also evidence that people infected with herpes viruses may be at greater risk for salivary gland tumors. And individuals infected with human immunodeficiency virus (HIV) have more salivary gland disease in general, and may be at greater risk for salivary gland tumors.

Although there has been speculation that the electromagnetic fields generated by cell phones increase the risk of salivary gland tumors, a recent study done in Denmark has concluded that the use of cell phones, pagers, and similar devices is not a risk factor.

Symptoms are often absent until the tumor is large or has metastasized (spread to other sites). In many cases, the tumor is first discovered by the patient's dentist. During regular dental examinations, the dentist

looks for masses on the palate or under the tongue or in the cheeks, and such checkups are a good way to detect tumors early. Some symptoms are:

- lump or mass in the mouth
- swelling in the face
- pain in the jaw or the side of the face
- difficulty swallowing
- difficulty breathing
- difficulty speaking

Diagnosis

A tissue sample will be taken for study via a **biopsy**. Usually an incision is necessary to take the tissue sample. Sometimes it is possible to take a tissue sample with a needle.

Magnetic resonance imaging (MRI) and **computed tomography** (CT) scans are also used to evaluate the tumor. They help determine whether the cancer has spread to sites adjacent to the salivary gland where it is found. MRI offers a good way to examine the tonsils and the back of the tongue, which are soft tissues. CT is used as a way of studying the jaw, which is bone.

Treatment team

Generally, physicians with special training in the organs of the nose and throat take responsibility for the care of a patient with a salivary gland cancer. They are called otolaryngologists or occasionally by a longer name, otorhinolaryngologists.

For short, otolaryngologists are usually labeled ENT (for Ear, Nose and Throat) specialists. An ENT specializing in cancer will probably lead the team. An oncologist or radiation therapist may be involved, and nurses, as well as a nutritionist, speech therapist and social worker, will also be part of the team. Depending on the extent of the cancer when diagnosed, some surgery and treatments result in extensive changes in the throat, neck and jaw. The social worker, speech therapist and nutritionist are important in helping the patient cope with the changes caused by surgery and radiation treatment. If there is great alteration to the neck because of surgery, rehabilitation will also be part of the recovery process and a rehabilitation therapist will become a member of the team.

Clinical staging, treatments, and prognosis

To assess the stage of growth of a salivary gland tumor, many features are examined, including how big it is and the type of abnormal cell growth. Analysis of the types of abnormal cell growth in tissue is so specific that many salivary gland tumors are given unique names.

In stage I cancer the tumor is less than one inch in size and it has not spread. Stage II salivary gland cancers are larger than one inch and smaller than two and one-half inches, but they have not spread. Stage III cancers are smaller than one inch, but they have spread to a lymph node. Stage IV cancers have spread to adjacent sites in the head, which may include the base of the skull and nearby nerves, or they are larger than two and one-half inches and have invaded a lymph node.

Surgical removal (excision) of the tumor is the most common treatment. **Chemotherapy** and radiation therapy may be part of the treatment, particularly if the cancer has metastasized, or spread to other sites; chemotherapy of salivary gland cancers, however, does not appear to extend survival or improve the patient's quality of life. Because there are many nerves and blood vessels near the three major pairs of salivary glands, particularly the parotids, the surgery can be quite complicated. A complex surgery is especially true if the tumor has spread.

A promising form of treatment for patients at high risk of tumor recurrence in the salivary glands near the base of the skull is gamma knife surgery. Used as a booster treatment following standard neutron radiotherapy, gamma knife surgery appears to be well tolerated by the patients and to have minimal side effects.

Tumors in small salivary glands that are localized and can usually be removed without much difficulty.

KEY TERMS

Adenoids—Common name for the pharyngeal tonsils, which are lymph masses in the wall of the air passageway (pharynx) just behind the nose.

Biopsy—Tissue sample is taken from the body for examination.

Computed tomography (CT)—X rays are aimed at slices of the body (by rotating equipment) and results are assembled with a computer to give a three-dimensional picture of a structure.

Lymph—Tissue that is part of the lymphatic system, the system that collects and returns fluid to the blood vessels and produces substances that fight infection.

Magnetic resonance imaging (MRI)—Magnetic fields and radio frequency waves are used to take pictures of the inside of the body.

Tonsils—Common name for the palatine tonsils, which are lymph masses in the back of the mouth, on either side of the tongue.

The outlook for survival once the tumor is removed is very good if it has not metastasized.

For parotid cancers, the five-year survival rate is more than 85% whether or not a lymph node is involved at diagnosis. The ten-year survival rate is just under 50%.

Most early stage salivary gland tumors are removed, and they do not return. Those that do return, or recur, are the most troublesome and reduce the chance an individual will remain cancer-free.

Alternative and complementary therapies

Such techniques as yoga, meditation, or biofeedback can help a patient cope with anxiety over the condition and discomfort from treatment and should be explored as an option.

Coping with cancer treatment

A support group helps during the course of treatment and follow-up. Patients are encouraged to join one. They should also be encouraged to take an active role in following the recommendations and decisions made by the treatment team.

Clinical trials

There are a number of **clinical trials** in progress. For example, the more researchers understand the nature of cancer cells, the better they are able to design drugs that attack only cancer cells. Or, in some cases, drugs that make it easier to kill cancer cells have also been designed.

The Cancer Information Service at the National Institutes of Health offers information about clinical trials that are looking for participants. The service can be contacted at (800) 422-6237.

QUESTIONS TO ASK THE DOCTOR

- Which type of salivary gland tumor do I have?
- Is this the best place to have the salivary gland tumor treated?

Prevention

Minimizing intake of alcoholic beverages may be important. Avoiding unnecessary exposure of the head to radiation may also be considered preventative. Anything that reduces the risk of contracting a sexually transmitted disease, such as the use of condoms, also may lower the risk of salivary gland cancer.

Special concerns

Salivary gland tumors are considered rare. Because there are so many salivary glands, and so many types of salivary tumors, most physicians (even those who specialize in diseases of the ears, nose and throat) are challenged when they must interpret results of study of tumor tissue. For treatment of a salivary gland tumor, it is best to find a medical facility that specializes in diseases of the head and neck. Such a facility will be better able to match treatment to the specific characteristics of the tumor.

See also Oral cancer; Oropharyngeal cancer.

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Diane M. Calabrese
Rebecca J. Frey, PhD

Samarium SM 153 Lexidronam *see* **Radiopharmaceuticals**

Sarcoma

Definition

A general term for any cancer of the bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissues. Sarcomas can be divided into soft tissue and bone (osteogenic) sarcomas. Liposarcomas (cancerous tumors of fat tissue) are an example of soft tissue sarcomas, while **Ewing's sarcoma** is considered an osteogenic sarcoma.

Kate Kretschmann

Sargramostim

Definition

Sargramostim is a medicine used to increase the blood cell counts after bone marrow transplants and **chemotherapy**. Sargramostim may be referred to as GM-CSF or granulocyte-macrophage colony stimulating factor.

Purpose

Sargramostim is a drug approved by the Food and Drug Administration (FDA) to decrease the time it takes for the bone marrow blood counts to recover after a bone marrow transplant. This decreases the risk of infection, the amount of time patients are treated with **antibiotics**, and the amount of time patients are in the hospital

Sargramostim is approved for use after chemotherapy to increase the recovery of the white cell counts and decrease the length of time a patient may have a **fever** and infection due to a low white count.

Sargramostim can be used after **bone marrow transplantation**. Once the new healthy bone marrow has been given back to a patient, sargramostim can be administered to help increase the blood cell counts and decrease the risk of fever and infection. Sargramostim can be used in patients when bone marrow is not recovering after a bone marrow transplant.

Sargramostim can be used for patients who will undergo a peripheral blood stem cell transplant. Patients will receive the sargramostim before the transplant. The sargramostim in these patients causes young, non-developed blood cells, known as stem or progenitor cells, to move from the bone marrow to the blood where they will then be removed from a patient by the process of apheresis. These blood cells are stored until after the patient receives larges doses of chemotherapy that destroy the bone marrow and the cancer. The patient then receives these stored cells back by an intravenous infusion. The stored cells repopulate the bone marrow and develop into the many types of functioning blood cells.

Description

Sargramostim is known as the brand name Leukine or Prokine. It has been available for use in bone marrow transplant patients for almost a decade. In cancer patients, chemotherapy destroys white blood cells temporarily. These white blood cells will grow again, but during the time that the levels are low patients are at an increased risk of developing fevers and infection. Sargramostim acts to stimulate the bone marrow to make more white blood cells which can either prevent the white count from dropping below normal or decrease the time

that the level is low. This helps the patient avoid fevers and infections and allows them to receive their next doses of chemotherapy without delay.

Recommended dosage

Sargramostim is a clear colorless liquid that is dosed based on a mathematical calculation that measures a person's body surface area (BSA). This number is dependent on a patient's height and weight. The larger the person the greater the body surface area. Body surface area is measured in the units known as square meter (m^2). The body surface area is calculated and then multiplied by the drug dosage in milligrams per square meter (mg/m^2). This calculates the actual dose a patient is to receive.

It is kept refrigerated until ready to use and it is administered to patients as an injection directly underneath the skin, subcutaneously. Subcutaneous is the preferred way to give the drug; it can be given in the back of the arms, upper legs, or stomach area. Sargramostim can also be administered to patients as a short intravenous infusion into a vein over 15 to 30 minutes.

To treat chemotherapy caused neutropenia in AML patients

The starting dose for AML patients who have just finished induction chemotherapy is 250 micrograms per square meter per day. This is given beginning four days after the chemotherapy has ended or approximately day number eleven of therapy. The dose is administered as intravenous infusion over a period of four hours. The doctor will inform the patient when it is time to stop the sargramostim based on blood count monitoring.

For patients receiving bone marrow transplant

The recommended dose is 250 micrograms per square meter per day administered as a two-hour infusion intravenously. This medication should begin within 2 to 4 hours of the patient receiving the bone marrow infusion.

If the patient's counts are not returning after the bone marrow has been received, sargramostim can be administered at a dose of 250 micrograms per square meter per day intravenously over a two hour time period for 14 consecutive days. This can be repeated after a seven-day rest for two more cycles. The doctor may increase the dose to 500 micrograms per square meter per day if the white count does not rise.

For patients prior to receiving a peripheral blood stem cell transplant

The recommended dose is 250 micrograms per square meter per day. This can be given either as a once daily dose administered under the skin, or intravenously administered as a continuous infusion over 24 hours. This dosing should continue until the last day of collection.

For patients after receiving a peripheral blood stem cell transplant

The recommended dose is 250 micrograms per square meter per day. This can be given either as a once daily dose administered under the skin, or intravenously administered as a continuous infusion over 24 hours. This dosing should begin right after the patient receives the stem cell infusion and continue until the white count rises to acceptable levels.

Precautions

Sargramostim should not be received by a patient in the 24-hour time frame before or after receiving chemotherapy.

Blood counts will be monitored frequently while on sargramostim. This allows the doctor to determine if the drug is working and when to stop treatment.

Sargramostim can affect patients who have kidney or liver problems before beginning treatment. These patients will be monitored by the doctor for any changes in kidney or liver function.

It is not recommended to give sargramostim to patients who have certain types of leukemias.

Sargramostim should be used with caution in patients who have fluid problems, including heart and lung problems.

Patients with a known previous allergic reaction to sargramostim or yeast-derived substances should tell their doctor before receiving this drug.

Patients who may be pregnant or trying to become pregnant should tell their doctor before receiving sargramostim.

Side effects

One of the most common side effects of sargramostim is **bone pain**. The sargramostim causes bone marrow to produce more white blood cells, and the process causes the patient to experience pain in their bones.

Other common side effects due to sargramostim administration are fever, muscle aches, chills, and weakness.

An uncommon, but serious side effect of sargramostim is increased fluid in patients. This swelling with fluid can occur in the body as a whole, legs, arms, around the heart, and in the lungs.

KEY TERMS

Antibiotics—Specific drugs used to treat infections.

Apheresis—The process of removing and collecting specific cells from the blood through a machine.

Bone marrow transplant—A procedure that destroys all of a patient's diseased bone marrow and replaces it with healthy bone marrow.

Chemotherapy—Specific drugs used to treat cancer.

Intravenous—Entering the body directly through a vein.

Food and Drug Administration (FDA)—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives the approval to pharmaceutical companies for commercial marketing of their products.

Neutropenia—A condition involving low levels of the white blood cells responsible for fighting infections.

Peripheral blood stem cell transplant—A procedure that collects and stores healthy young and non-developed blood stem cells. These are then given back to a patient to help them recover from high doses of chemotherapy.

Reinfusion—The transfer through a vein of healthy stem cells or bone marrow to a patient that has received large doses of chemotherapy.

Subcutaneous—Underneath the initial layer of skin.

Patients who have received sargramostim treatment have reported: **nausea and vomiting**, muscle pain, abdominal pain, rash, **diarrhea**, hair loss (alopecia), mouth sores, **fatigue**, allergic reactions and **itching**, shortness of breath, weakness, dizziness, heart problems, pain at the injection site, blood clots, headache, cough, rash, constipation, and change in kidney and/or liver function. These side effects may be due to the chemotherapy administration patients have received prior to the sargramostim.

Interactions

Sargramostim should not be given at the same time as chemotherapy or **radiation therapy**. Dosing should begin at least 24 hours after the last dose of treatment.

Patients on lithium or steroids should tell their doctor before starting sargramostim therapy, as these drugs can affect the white blood cell count.

Nancy J. Beaulieu, RPh.,BCOP

Saw palmetto

Definition

Saw palmetto is a natural plant remedy used to treat men who are experiencing difficulty when urinating. According to the American Dietetic Association, saw palmetto is one of the most commonly used dietary supplements among Americans between the ages of 50 and 76.

Purpose

Saw palmetto is not used to treat cancer. It is used to treat non-malignant enlargement of the prostate gland, also called benign prostatic hyperplasia (BPH).

Although saw palmetto has also been used to treat prostatitis and chronic pelvic pain syndrome (CPPS) in men, it does not appear to be useful for these conditions. A group of researchers at Columbia University reported in early 2004 that men given saw palmetto for CP/CPPS showed no appreciable improvement at the end of a year-long trial.

Description

The prostate gland is found only in men. It is located where the bladder drains into the urethra. The urethra is the tube that takes urine out of the body. The prostate gland contributes to the fluid in which sperm are ejaculated (semen).

It is common for the prostate to enlarge in men over age 50. This enlargement often is not malignant. It is thought to occur because of the action of **testosterone**, a male hormone, on the cells of the prostate. As the prostate grows, it can press on the urethra and narrow it. This causes men to have problems with urination that include the frequent urge to urinate (especially at night) and a week, dribbling, interrupted urine stream.

Saw palmetto is the bushy palm, *Serenoa repens* that grows to a height of about 18 feet (6 m) along the coast of the United States from South Carolina to Florida, and in Southern California. It is also found in Europe along the Mediterranean. Other names for this plant are American dwarf palm, cabbage palm, serenoa, or sable. The

medicinal part of the saw palmetto is an extract from the dark, olive-sized berries.

Saw palmetto has a long history of use by Native Americans in treating bladder inflammation, urinary difficulties, sexual difficulties, and respiratory tract infections. Of these uses, the only scientifically substantiated claim is that saw palmetto eases urinary difficulties and increases urine output. Although the exact mechanism of action of saw palmetto has not been determined, it is believed to interfere with the action of testosterone on the prostate gland. Finasteride (Proscar, also known as Permixon) is a prescription drug used to treat BPH that works in the same way. It is important to remember that BPH is not cancer, and saw palmetto is not a treatment for cancer.

Recommended dosage

Extract of saw palmetto is available in health food stores in capsules, liquid concentrate, tablets, and as dried, ground berries. An average daily dose of the drug is 1–2 grams of which 320 mg are the active ingredients. Dosage may vary from manufacturer to manufacturer.

Saw palmetto is classified as a dietary supplement. The United States Food and Drug Administration does not test or certify it. Unlike traditional pharmaceuticals, its manufacture is largely unregulated. Dietary supplements such as saw palmetto are not required to meet standards of purity or effectiveness in controlled **clinical trials**. Men interested in using saw palmetto should look for a reputable manufacturer of supplements who provides adequate testing and label information. The cost of dietary supplements is not covered by insurance.

Precautions

Men who are having trouble urinating should see a doctor before taking any remedies on their own. **Prostate cancer** is a serious, sometimes life-threatening disease, and its symptoms can be similar to BPH. A blood test and physical examination are used to diagnose prostate cancer. It is believed that saw palmetto may interfere with this blood test (called a prostate specific antigen or PSA test). Men should have this blood test done before they begin taking saw palmetto to make sure they get correct results.

Side effects

Saw palmetto has few side effects, and is generally regarded as safe. Medical authorities in Germany, France, and Italy all officially recognize it as a safe and generally effective treatment for symptoms of BPH. Side effects that have been reported are uncommon but include headache, upset stomach, and **diarrhea**.

KEY TERMS

Malignant—Cancerous. Cells tend to reproduce without normal controls on growth and form tumors or invade other tissues.

Testosterone—The main male hormone. It is produced in the testes and is responsible for the development of primary and secondary male sexual traits.

Interactions

Since saw palmetto is a natural remedy, few controlled studies have been done on how it interacts with other herbal remedies or traditional pharmaceuticals. In general, however, persons taking birth control pills, estrogen replacement therapy, or testosterone replacement therapy should consult their doctor before taking saw palmetto.Patients taking any supplements such as **vitamins** or herbs should tell their doctor.

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Tish Davidson, AM
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Scintigraphy *see* **Nuclear medicine scans**

Scopolamine

Definition

Scopolamine, also called hyoscine hydrobromide, is used in cancer treatment to prevent **nausea and vomiting** that results from movement of the head.

Purpose

Chemotherapy causes nausea and vomiting in many people. These conditions can occur for several different reasons. Scopolamine is used to treat nausea and vomiting that result from movement of the head. In many ways, this type of nausea is similar to motion sickness.

Other uses of scopolamine include pre-anesthesia sedation. In combination with morphine, scopolamine may be given to women in childbirth to induce "twilight sleep." Lastly, scopolamine is used in an ophthalmic solution to dilate the pupil of the eye before an eye examination.

Description

Scopolamine is a natural product and is familiar to many people as a motion sickness medicine. In its most common form, it comes as a patch that a person with motion sickness wears behind the ear. It is also known by the brand names Transderm-Scop and Transderm-V.

As a motion sickness drug, scopolamine has been used for many years with few side effects. It is approved by the United States Food and Drug Administration (FDA), and its cost is usually covered by insurance. In cancer treatment, scopolamine is used to treat a particular type of nausea and vomiting that occur as a result of chemotherapy.

Scopolamine is classified as an anticholinergic drug. This means it works by blocking the nerve impulses that send information from the part of the inner ear that controls the sense of balance. In motion sickness, a person vomits because conflicting information arrives in the brain from the inner ear and the eye. Some chemotherapy drugs also cause the brain to receive conflicting information, so that when patients move their head, they feel nauseated. People vary in their sensitivity to this condition. This drug is effective in helping most people control nausea and vomiting that arises from this source.

Recommended dosage

Scopolamine comes in a patch that the patient applies behind the ear. The patch stays in place for three days and releases a continuous supply of the drug. To be effective, the patch must be applied at least four hours before chemotherapy is begun. After three days, the patch is removed. Unused patches should be stored at room temperature.

KEY TERMS

Narrow-angle glaucoma—Glaucoma is a disease where increased pressure in the eye causes damage and changes to the field of vision. Narrow-angle refers to a specific type of damage.

Precautions

People applying or removing a scopolamine patch should wash their hands well immediately after handling the patch so that they do not accidentally transfer any of the drug to other parts of their body (for example, by rubbing their eyes). Scopolamine should not be used in children, should be kept away from pets, and should be used with caution in the elderly.

The patch should be used with caution in patients with a history of either seizures or psychosis, because scopolamine may make either of these disorders worse.

Side effects

About 65% of the people who use scopolamine get a dry mouth. About 17% of people report feeling drowsy from the drug. Other less common side effects include blurred vision, disorientation, restlessness, confusion, dizziness, difficulty urinating, constipation, skin rash, dry red itchy eyes, extreme sensitivity to light, and narrow-angle glaucoma.

Interactions

Many drugs interact with nonprescription (over-the-counter) drugs and herbal remedies. Patients should always tell their health care providers about these remedies, as well as prescription drugs they are taking. Patients should also mention if they are on a special diet such as low salt or high protein.

Scopolamine interferes with the absorption of ketoconazole (Nizoral), an antifungal drug, sometimes used to treat **prostate cancer**. It may also interact with other anticholinergic drugs (drugs that block nerve impulses), antidepressants, and antihistamines. Scopolamine decreases the absorption of phenothiazines (antipsychotic drugs), and interfers with the effectiveness of levodopa, a drug given to treat Parkinson's disease.

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United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

Tish Davidson, A.M.
Rebecca J. Frey, PhD

Screening test

Definition

A screening test is a procedure that is performed to detect the presence of a specific disease. The individual or group of individuals (as in mass screenings) does not present any symptoms of the disease.

Purpose

The purpose of a cancer screening test is to identify the presence of a specific cancer in an individual that does not demonstrate any symptoms. Screening allows for early detection of cancer and can save the life of the person who might have died if the cancer was not detected by screening. If cancers are detected early, the treatment can be more effective and often less costly than if the cancer had progressed and needed drastic treatment.

KEY TERMS

BRCA-1 and BRCA-2—These are tumor suppressor genes whose inherited mutations have been associated with hereditary forms of breast cancer.

Digital rectal exam—The physician will feel the prostate for irregular symmetry by going into the rectum.

Genetic test—This tests for the presence of specific genes or the presence of mutations on specific genes.

Prostate-specific antigen test—This test measures the level of prostate antigen in the blood to identify presence of prostate cancer.

Transrectal ultrasonography—This test uses a small rectal probe to create an image of the prostate gland.

Precautions

Most screening tests have been developed to be non-invasive or mildly invasive. For example breast self-exams, mammograms, and pelvic exams may be uncomfortable but are non-invasive. Therefore, most screening tests will not be affected by medications that a patient may be taking or other unrelated conditions a patient may be experiencing.

Description

Before developing or administering a screening test, the effectiveness of the test needs to be evaluated. There are several criteria to consider when deciding whether or not to screen. First, is the cancer highly fatal and common? If yes, then it is suitable for screening. Second, in order to screen a cancer, there must be detectable pre-symptomatic indicators. Finally, the reliability of results needs to be evaluated. A test can have one of the four following outcomes: true positive, false positive, true negative, and false negative. Randomized controlled trials also help to identify effective screening.

Screening tests exist for many of the more common cancers such as **prostate cancer**, **breast cancer**, **colon cancer**, lung cancer, and **cervical cancer**. Each screening test has an advisable age to begin screening and a recommended frequency at which the test should be performed. As people age, cancer becomes more prevalent; therefore, more screening tests are recommended.

Prostate cancer screening

Prostate cancer affects many men each year. Screening includes a digital rectal exam, tests for

prostate-specific antigen (PSA), and transrectal **ultrasonography** (TRUS). Each of these tests takes less than half an hour to perform. The PSA test is an excellent tool as it is highly sensitive, reasonably priced, and well-tolerated by patients. Men should be counseled about the benefits and risks of detecting and treating an indolent tumor (this cancer may not have caused symptoms). The treatment may cause urinary and sexual problems.

Breast cancer screening

After skin cancer, breast cancer is the most common malignancy that is diagnosed in women. There are several screening methods that can be performed, including **breast self-exam** (performed by the patient), clinical breast exam, **mammography**, and BRCA-1 and BRCA-2 **genetic testing**. Genetic testing is offered to patients who have a familial history of breast cancer. All of these tests can be performed in the doctor's office and take less than half an hour. Genetic testing requires a blood sample, and it takes a few days to receive the results. Counseling is strongly advised prior to genetic testing.

Colon cancer

Colon cancer (colorectal cancer) is the third leading cause of cancer death in the United States and is the third most diagnosed cancer among both men and women. Screening tests include **fecal occult blood test**, flexible **sigmoidoscopy**, **barium enema**, and **colonoscopy**. High-risk patients (significant familial history) should begin screening at puberty or 10 years prior to occurrence of family member's tumor. Sigmoidoscopy and colonoscopy are slightly invasive, completed under mild sedative in the hospital on an outpatient basis, and take about 15 and 30 minutes respectively. Screening with colonoscopy is unique and reliable, because it allows visualization of the entire colon.

Preparation

Most screening procedures are non-invasive in order to make them convenient for patients and cost effective. Screening such as breast exams, mammography, pelvic exams, digital rectal exams, and tests that require blood samples require no preparation by the patient. However, barium enema, sigmoidoscopy, and colonoscopy all require prior preparation of the bowel. Patients will be asked to consume a clear liquid diet 24 hours prior to the exams, followed by liquid laxative about 2 hours prior to the exam. An enema or two may be required until the stool is clear.

Aftercare

Since most of the exams are non-invasive, there is no required aftercare. However, patients are encouraged to monitor themselves for any related symptoms of the cancer in question.

QUESTIONS TO ASK THE DOCTOR

- What medications interfere with the results of this test?
- What tests can be performed to confirm that the results of this screening test are accurate?
- What is the most accurate and cost-effective screening test for the type of cancer in question?
- Can this test be performed anonymously?
- Will my insurance company pay for this test?

Risks

Since no medical tests are perfect, there are several negative consequences associated with screening. First, if a patient's prognosis would be the same with or without the screening, then the patient experiences a longer time of being sick. Second, if the results of the tests are a false negative, then the patient may be negligent in identifying symptoms and warning signals. Conversely if the results of the test are a false positive, then the patient may be subjected to unnecessary diagnostic procedures and psychological trauma. Finally, insurance companies or employers that possess results of a positive genetic test could use that information unethically, impacting coverage and employment advances.

Normal results

Normal results vary for each test and need to be analyzed for false negative results.

Abnormal results

Doctors schedule more diagnostic testing if abnormal results arise. Normally, a **biopsy** is administered on the tissue in question in order to view the cells for typical cancer traits.

See also Pap smear; Tumor grading; Tumor staging.

Resources

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Sally C. McFarlane-Parrott

KEY TERMS

Late effect—A consequence of illness or therapy that becomes evident only after long-term patient monitoring.

Neoplasm—A new, abnormal growth of tissue. A neoplasm may be benign or malignant.

Solid tumor—A cancer that originates in an organ or tissue rather than in bone marrow or the lymph system.

Second cancers

Definition

A second cancer is a malignancy that develops in someone who has survived an earlier cancer.

Description

Formally referred to as second primary neoplasms, second cancers are also described as late effects of the original disease or of the treatment used to cure it.

Blood-based malignancies usually occur within a few years of treatment. Solid tumors may not become evident until 20 years later. Most second cancers affect parts of the body that have been exposed to radiation and are near the site of the original tumor.

Demographics

Having once had cancer almost doubles an individual's risk of having cancer a second time. A child who develops cancer before the age of 15 is eight times more susceptible to a new cancer than a boy or girl the same age who has not had the disease. Age does not seem to decrease the likelihood that any cancer survivor will develop a second malignancy.

Each year, almost 100,000 new malignancies are diagnosed among the more than 8,000,000 children, teenagers, and adults who have previously been treated for cancer. Although still rare, the incidence of new cancers in patients cured of one or more malignancies more than doubled (from approximately 6.4% to 15.3%) between 1973 and 1997. The rate of second cancers will continue to rise as the number of long-term cancer survivors continues to grow.

Children who have been treated for **Hodgkin's disease** are most at risk for developing a second cancer within 20 years. The likelihood is lowest for individuals who survive five years or longer after being treated for non-Hodgkin's **lymphoma**.

Causes

Some second cancers result from the risk factors responsible for the original disease. Some are caused by radiation or **chemotherapy** treatments that damage normal cells or suppress the patient's immune system.

Chemotherapy generally increases the likelihood of leukemia. Radiation raises the risk of developing **breast cancer** or other solid tumors.

Scientists do not fully understand why chemotherapy causes some cancer survivors to develop new malignancies. They believe radiation's role in second cancers is influenced by:

- the kind of radiation exposure the patient receives
- how much radiation the patient receives
- how old the patient is at the time of treatment
- the patient's personal and family medical history

Research

Although second cancers can occur following treatment for any type of cancer, researchers are concentrating on lymphoma, leukemia, and testicular cancer because these are the diseases that most often affect children and young adults.

Researchers are also trying to determine which types of cell damage can be characterized as precancerous and how:

- the patient's gender
- the patient's age at the time of diagnosis
- the stage of the original cancer at the time of diagnosis
- the length of the patient's survival affect the risk of developing a second cancer.

Other studies focus on whether administering both radiation and chemotherapy raises or lowers a patient's risk of developing a second cancer and how specific chemotherapy drugs, the number of times a patient is exposed to radiation, and the total amount of radiation a

patient receives during a course of treatment affect the chances of developing a new malignancy.

In 1993, the National Cancer Institute (NCI) initiated the Childhood Cancer Survivor Study (CCSS). The most extensive study of its kind ever undertaken, the ongoing investigation involves more than 20,000 patients diagnosed with cancer before the age of 21. It is designed to:

- provide new information about long-term effects of cancer and cancer treatments
- enable doctors to design treatments that increase survival rates and reduce the incidence and severity of unpleasant or harmful side effects
- help survivors understand how diagnosis and treatment can continue to affect their health
- implement programs for the prevention and early detection of second cancers and other late effects

In 1996, NCI established an Office of Cancer Survivorship (OCS) to identify and provide education and support for the special physical and emotional needs of cancer survivors.

OCS's mission is improving cancer survivors' quality of life. Priority research focuses on increasing awareness of the challenges associated with cancer survivorship and developing programs to lessen the burdens of cancer survivors.

NCI's Pediatric Oncology Branch conducts **clinical trials** for children whose cancer has recurred or has not responded to treatment.

Prevention

Researchers are:

- investigating the process that transforms cancer treatments into sources of new tumors
- studying ways to maintain or improve survival rates while treating patients with gentler types of chemotherapy or doses of radiation too low to inflict the cell damage that causes second cancers
- confident that further research into causes of second cancers will enable them to develop strategies to prevent the development of new malignancies

Even though only a small percentage of cancer survivors develop second malignancies, everyone who has had cancer must:

- follow a healthy lifestyle
- avoid known causes of cancer, like smoking or prolonged exposure to the sun
- diligently follow their doctor's recommendations regarding cancer screenings and other forms of medical surveillance

QUESTIONS TO ASK THE DOCTOR

- Am I likely to develop a second cancer?
- How can I reduce my risk of developing a second cancer?
- What symptoms might mean that I have developed a new cancer?
- What should I do if any of these symptoms occur?

- see a doctor as soon as they develop new symptoms or notice any changes in the way they look or feel

Special concerns

Improved long-term cancer survival rates have increased concern about the physical and psychological effects of the disease and the treatments used to cure it.

Doctors must monitor cancer patients carefully to make sure radiation and chemotherapy dosages low enough to eliminate unwanted side effects are strong enough to eradicate all a patient's cancer cells.

A patient who has had cancer should be aware of the risk of developing a second cancer. However, patients should not refuse or discontinue treatment for fear of developing a second malignancy. The benefits of cancer treatment far outweigh the risk of developing a new cancer.

Resources

ORGANIZATIONS

Division of Cancer Control and Population Sciences, National Cancer Institute. 6130 Executive Blvd., Executive Plaza North, Rockeville, MD 20852. (301) 594-6776. <http://dccps.nci.nih.gov/ocs>.

National Childhood Cancer Foundation.440 E. Huntington Dr., PO Box 60012, Arcadia, CA 91066-6012. (800) 458-NCCF. <http://www.nccf.org/NCCF/Advocacy/program.asp>.

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Maureen Haggerty

Segmentectomy

Definition

Segmentectomy is the excision (removal) of a portion of any organ or gland. The procedure has several variations and many names, including wide excision, **lumpectomy**, tumorectomy, quadrantectomy, and partial **mastectomy**.

Purpose

The purpose of this procedure is to surgically remove a portion (in this case, with a cancerous tumor) of an organ or gland as a treatment.

Precautions

Because of the need for radiotherapy after segmentectomy, some patients, such as pregnant women and those with syndromes not compatible with radiation treatment, may not be candidates for this procedure. As with any surgery, patients should alert their physician about all allergies and any medications they are taking.

Description

Common organs that have segments are the breasts, lungs, and liver. When cancer is confined to a segment, removal of that portion may offer cancer-control results equivalent to larger operations. This is especially true for breast and liver cancers. In cases of lung cancer, **lobectomy** (surgical removal of all or part of the lung) is preferable, but if the patient does not have sufficient pulmonary function to tolerate this larger operation, then a segmentectomy may be necessary. For breast and lung cancers, this procedure is often combined with removal of some or all regional lymph nodes.

Preparation

Routine preoperative preparations, such as having nothing to eat or drink the night before surgery, are typically ordered for a segmentectomy. Information about expected outcomes and potential complications is also part of the preparation for this surgery.

Aftercare

After a segmentectomy, patients are usually cautioned against any moderate lifting for several days. Other activities may be restricted (especially if lymph nodes were removed) according to individual needs. Pain is often enough to limit inappropriate motion. Women who undergo segmentectomy of the breast are often instructed to wear a well-fitting support bra both day and night for approximately one week after surgery. Pain is usually well-controlled with prescribed medication. If it is not, the patient should contact the surgeon, as severe pain may be a sign of a complication, which needs medical attention.

Radiation therapy is usually started four to six weeks after surgery and will continue for four to five weeks. The timing of additional therapy is specific to each individual patient.

KEY TERMS

Conservation surgery—Surgery that preserves the aesthetics of the area to be worked on.

Excision—To surgically remove.

Lymph nodes—Small, bean-shaped organs located throughout the lymphatic system. Lymph nodes store special cells that can trap cancer cells and bacteria that are traveling through the body.

Radiotherapy—The treatment of disease with high-energy radiation, such as x or gamma rays.

Risks

Risk of infection in the area affecting a segmentectomy only occurs in 3% to 4% of patients.

Normal results

Successful removal of the tumor.

Abnormal results

Major bleeding and/or infection at the wound after surgery.

Clinical Trials

Using a segmentectomy to remove breast cancers (as a technique that conserves the aesthetics of a breast) is being investigated for large tumors after several cycles of preoperative **chemotherapy**. Segmentectomy is also being investigated for treating small-cell lung cancers. Information about clinical trial options is available from the National Cancer Institute at <http://www.nci.nih.gov>.

Resources

BOOKS

Zurrida, S., and Giovanna Gatti. "Breast Conservation: Quandrantectomy: Its Current Role and Technical

QUESTIONS TO ASK THE DOCTOR

- Is segmentectomy an option for treatment?
- How will I know that all the cancer has been removed?
- What is the risk of tumor recurrence if I undergo this procedure?
- What should I do to prepare for surgery?
- What future care will I need?

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Laura Ruth, Ph.D.

Self image *see* **Body image/self image**

Semustine

Definition

Semustine, also known as methyl-CCNU, is one of a group of antineoplastic (antitumor) drugs known as alkylating agents. As of mid-2001, it was an **investigational drug**.

Purpose

Semustine has been used in the treatment of brain tumors, lymphomas, colorectal cancer, and **stomach cancer**. It is not clearly superior to other treatments for these diseases. It has also been associated with an increased risk of secondary (that is, treatment-related) leukemia. Thus, semustine is not widely used in the U.S.

Description

Like many antineoplastic (antitumor) therapies, semustine acts by killing quickly growing cells. Since cancerous cells are generally growing faster than normal cells, drugs that kill quickly growing cells generally affect tumors more than normal cells. However, some normal cells, such as white blood cells and platelets, also grow quickly, and can be severely affected by antineoplastic drugs. Antitumor therapies create a situation where the drug is racing to kill the tumor before it causes irreparable damage to normal tissues. The ideal situation is one in which the growth of the tumor is severely affected, but the growth of normal cells is unaffected. However, not every situation is ideal. Some patients taking antitumor drugs may have to discontinue treatment or decrease the dose because of side effects.

Semustine is included in the group of anticancer drugs known as alkylating agents.

Semustine is an investigational drug in the United States. This means that the FDA has not approved this drug for marketing in the U.S. as of mid-2001. Generally, investigational drugs are made available through participation in research studies.

Many drugs have toxic side effects, some of which are difficult to detect. **Clinical trials** are used to determine the side effects, drug interactions, and precautions for medicines, as well as their efficacy. Successful completion of multi-step clinical trials results in FDA approval of a drug. Many drugs that are used in clinical trials never gain FDA approval, however, possibly because of severe side effects that outweigh the benefits of the medication, or because the medication does not perform the function for which it was tested. Final approval of a drug is also expensive. Some drugs may not receive the financial support necessary to achieve final approval.

Recommended dosage

Since semustine is investigational, there is no recommended dosage. Different dosing schedules have been reported in the literature for different cancers.

Precautions and side effects

In the published reports of semustine use, a common side effect is **myelosuppression**, the damage to white

KEY TERMS

Investigational drug—A drug that has not been approved for marketing by the FDA. These drugs are generally available to patients through participation in research studies.

blood cells and platelets. Such damage may result in infection and bleeding, respectively. The myelosuppression from semustine is prolonged, meaning that it takes longer for blood cells to recover than is seen with many other anticancer drugs. Therefore, the interval between courses of semustine is longer than with other agents. Semustine also causes **nausea and vomiting**. Sometimes **anorexia**, or loss of appetite, persists after nausea and vomiting. As noted above, semustine has also been associated with the development of secondary leukemia.

Interactions

As of mid-2001, information on the interactions of semustine is not available.

Michael Zuck, Ph.D.

Senna *see* **Laxatives**

Senokot *see* **Laxatives**

Sentinel lymph node mapping

Definition

Sentinel lymph node mapping is a method of determining whether cancer has metastasized (spread) beyond the primary tumor and into the lymph system. The mapping procedure is used in conjunction with sentinel **lymph node biopsy** or dissection.

Purpose

The lymph system is the body's primary defense against infection. Lymph vessels carry clear, slightly yellow fluid called lymph that contains and proteins to help rid the body of infection. Lymph nodes are small, bean-shaped collections of tissue found along the lymph vessels. Cancer cells can break off from the original tumor and spread through the lymph system to distant parts of the body where secondary tumors are formed. One job of the lymph nodes is to clean the lymph by trapping foreign cells, such as bacteria or cancer cells, and identifying foreign proteins for antibody response.

The sentinel lymph node is the first lymph node that filters the fluid draining away from the primary tumor. If cancer cells are breaking off and entering the lymph system, the first filtering node (not necessarily the closest to the tumor) will be most likely to contain the breakaway cancer cells.

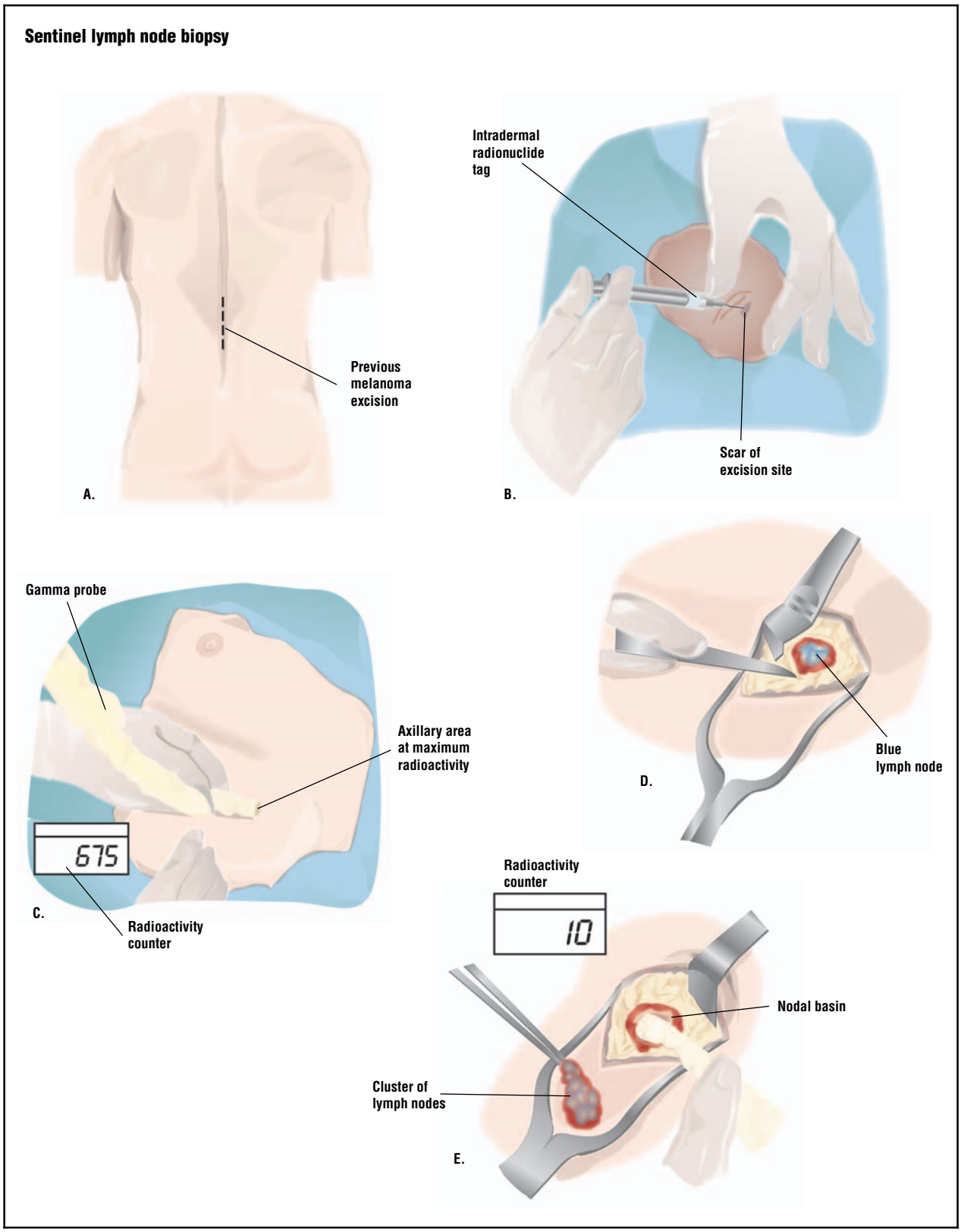
There are about 600 lymph nodes in the body. About 200 are in the head and neck and another 30–50 are in the armpit. Others are located in the groin. The sentinel node, or first filtering lymph node, will be different for each tumor and for each individual. Sentinel lymph node mapping is a technique for pinpointing which node is the most likely to receive the primary drainage from the tumor and therefore the most likely to contain cancer, so that it can be surgically removed and examined under the microscope for cancer.

If the sentinel node is cancer-free, there is a very high probability that cancer has not spread to any other node. If cancer cells are present in the sentinel node, it is likely that other nodes in the lymph system also contain cancer cells. This information is important in staging the cancer and individualizing cancer treatment for maximum benefit.

Sentinel lymph node mapping is a relatively new technique. It was first used in 1977 by researchers studying cancer of the penis. Later it was used successfully in staging **melanoma** (a type of skin cancer). In 1993, researchers first used the technique in **breast cancer** patients. Since then, **clinical trials** in breast cancer patients have demonstrated the accuracy and effectiveness of sentinel lymph node mapping and dissection in the staging of breast cancer. Researchers hope to be able to apply the sentinel node technique to other cancers in the future.

Advantages of sentinel lymph node mapping

Before sentinel node mapping was developed, there was no way of knowing whether and how far cancer had spread without removing and examining samples from many lymph nodes under the microscope. For example, in breast cancer patients, after a **lumpectomy** or **mastectomy** it was conventional treatment to remove most of the axillary nodes. These are the lymph nodes in the armpit. Removing axillary nodes causes frequent complications in as many as 80% of women. These complications include swelling (lymphedema), numbness, burning sensation in the armpit, reduction in arm and shoulder movement, and increased risk of infection.



(Illustration by Argosy Publishing. Reproduced by permission of the Gale Group.)

Sentinel **lymph node dissection** limits the extent of surgery. It provides the following advantages:

- Less surgical trauma because only one lymph node or a small cluster of nodes is removed. For example, in breast cancers, two or three nodes are generally removed.
- Fewer side effects from surgery.
- The lymph system is left intact and is better able to transport fluid and fight infection.
- Fewer risks of impairment of arm and shoulder movements.
- With only a small amount of tissue being removed, it can be studied much more exhaustively in the laboratory for the presence of cancer.
- Significant reduction in post-mastectomy pain.

How accurate are sentinel lymph node mapping and dissection?

In 2001, sentinel lymph node mapping is being used primarily in cases of melanoma and breast cancer. The technique is relatively new, and several breast cancer clinical trials are underway. One purpose is to determine the most accurate methods of finding the sentinel node. Another is to compare the control of cancer and survival rates of sentinel node **biopsy** with conventional axillary lymph node dissection in women whose sentinel nodes are both positive and negative for cancer. Up-to-date information about these clinical trials can be obtained from the National Cancer Institute at <http://www.cancertrials.nci.nih.gov> or (800) 4-CANCER.

Since sentinel lymph node mapping and dissection are relatively new, they are not done at every hospital. Doctors need special training in order to perform these procedures. Studies consistently have shown that the ability to locate the sentinel node increases the more experience doctors have with the procedure. Experienced physicians can pinpoint the sentinel node with about 95% to 98% accuracy. Similarly, studies have shown that there is a learning curve for surgeons and pathologists (doctors who examine the nodes in the laboratory) in sentinel lymph node dissection. The more experience they have, the more accurate they are.

Overall, accurate diagnoses from sentinel lymph node dissection are very high (92% or more). However, it is important that the patient find out how much training and experience the treatment team has with this procedure, and if necessary ask for a referral to another facility with more experienced staff. Some insurers may also consider the procedure experimental. Patients should check with their insurers about coverage, as the acceptance of this procedure is evolving.

KEY TERMS

Lumpectomy—Surgical removal of a tumor in the breast.

Lymph—Clear, slightly yellow fluid that carried by a network of thin tubes to every part of the body. Cells that fight infection are carried in the lymph

Lymph nodes—Small, bean-shaped collections of tissue found in lymph vessels. They produce cells and proteins that fight infection and filter lymph. Nodes are sometimes called lymph glands.

Lymph system—Primary defense against infection in the body. The tissues, organs, and channels (similar to veins) that produce, store, and transport lymph and white blood cells to fight infection.

Mastectomy—Surgical removal of the entire breast.

Metastasize—Spread of cells from the original site of the cancer to other parts of the body where secondary tumors are formed.

Precautions

Women with breast cancer who are the best candidates for sentinel node dissection are those with early stage breast cancer with low to moderate risk of lymph node involvement. Women who are not good candidates for sentinel node dissection are those who:

- Are believed to have cancer in the lymph nodes.
- Have had prior surgery (such as breast reduction surgery) that would change the normal pattern of lymph flow near the primary tumor.
- Have already received **chemotherapy**, because chemotherapy can create tissue changes that alter normal lymph flow.
- Are older, because lymph flow alters with age and the sentinel node may not be accurately detected. To get valid results, people with melanoma must have sentinel lymph node biopsy performed before wide excision of the original melanoma.

Description

Sentinel lymph node mapping and dissection is done in a hospital under general anesthesia. There are two methods of detecting the sentinel node. In the dye method, a vital blue tracer dye is injected near the tumor. The dye enters the lymph system and then collects in the sentinel or first filtering node. The surgeon looks for the accumulation of dye and removes the blue node.

In the radioactive technique, a low-level radioactive tracer is injected near the tumor. It is absorbed into the lymph system and travels to the sentinel node. A hand-held Geiger counter (a device that measures radioactivity) is passed over the area near the tumor until the spot with the most radioactivity is located. The radioactive ("hot") node is then removed. Because accuracy in locating the sentinel node is increased by 10% to 15% if both radioactive and dye tracers are used together, this is generally done.

Once the sentinel nodes are removed, they are sent to the laboratory to be examined for cancer. If no cancer cells are present, there is rarely a need to remove more lymph nodes. If cancer cells are present, it is likely that more lymph nodes will be removed. In any event, information from the sentinel node biopsy will be used to determine the best way to treat the cancer.

Preparation

Standard pre-operative blood and liver function tests are performed before sentinel node mapping and dissection. The patient will also meet with an anesthesiologist before the operation and should tell the anesthesiologist about all medication (prescription, non-prescription, or herbal) that he or she is taking and all drug allergies.

Aftercare

Since only a small amount of tissue is removed, patients generally recover quickly from sentinel node mapping and dissection. They may feel tired and from the anesthesia, and may experience minor burning, pain, and slight swelling at the site of the incision. If tracer dye is used, the dye stays in the body for up to nine months and may be visible under the skin.

Risks

The greatest risk associated with sentinel lymph node mapping is that the sentinel node cannot be identified and conventional removal of many lymph nodes will be necessary. Failure to locate the sentinel node happens in less than 5% of patients.

The second greatest risk is of a false-negative reading (approximately 5% to 8% for breast cancer), finding no cancer in the tissue sample when it is actually present. As discussed above, this test is extremely accurate when performed by an experienced treatment team.

Other risks associated with sentinel lymph node mapping are allergic reaction to the dye, infection at the incision site, and allergic reaction to anesthesia.

Normal results

If no cancer cells are found in the sentinel node, other lymph nodes do not need to be removed.

QUESTIONS TO ASK THE DOCTOR

- Am I a good candidate for sentinel lymph node mapping and biopsy?
- How much experience do you have with this procedure?
- If you have limited experience, can you refer me to a center where this operation is frequently performed?
- Where can I find out about clinical trials involving sentinel node mapping and biopsy?
- If I am not a good candidate for sentinel lymph node biopsy, why not, and what are my options?

Abnormal results

If cancer cells are found in the sentinel lymph node the treatment team may recommend an operation to remove more lymph nodes and/or radiation or chemotherapy to control the cancer.

Resources

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ORGANIZATIONS

American Cancer Society. National Headquarters, 1599 Clifton Rd. NE, Atlanta, GA 30329. 800 (ACS)-2345. <http://www.cancer.org>.

Cancer Information Service. National Cancer Institute, Building 31, Room 10A19, 9000 Rockville Pike, Bethesda, MD 20892. (800) 4-CANCER. <http://www.nci.nih.gov/cancerinfo/index.html>.

Tish Davidson, A.M.

Sexuality

Definition

Sexuality can be defined as the quality or state of being sexual. Quite often it is an aspect of one's need for closeness, caring, and touch.

Cancer and sexuality

Faced with a disease such as cancer most people initially lose interest in sex. Sexual desire is overshadowed by concern for one's health. Certain cancers directly affect sexual organs making sexual activity impossible or painful. **Chemotherapy**, radiation and surgical treatments of cancer can affect sexual activity making it difficult or undesirable. The side effects of cancer treatments such as nausea and pain can lessen sexual desire. Cancer treatments that disturb the normal hormone balance can also lessen desire. Many cancer patients are also worried that their partner may feel negatively about them because of the changes in their body and the fact that they have cancer.

Sexuality can be expressed in many different ways. It is possible to continue a healthy and satisfying relationship and maintain a healthy sexual image even after any changes brought about by cancer. Sexual intimacy can be a source of comfort during treatment and recovery from cancer. This may require some adaptation and change of the patient's current sexual patterns but with the right support groups and encouragement from the partner it should be possible to maintain healthy sexual activity.

Cancer and female sexuality

Women undergoing chemotherapy, **radiation therapy**, or pelvic surgery may experience pain during intercouse. This could be caused by changes in the size and moistness of the vagina, or infection of the bladder or vagina. Sometimes the pain is so severe that it sets off an involuntary contraction of the vagina called vaginismus. This contraction makes intercourse impossible. Extra lubrication is necessary to make intercourse comfortable. Vaginisimus can be treated by counseling and special relaxation training.

Radical surgery that will drastically change the physical aspects of the vagina and vulva pose an additional challenge for the affected woman and her partner. The woman may be affected psychologically by the change in appearance and also by the fear of pain or bleeding. The genitals may be physically altered so that sexual intercourse is difficult or impossible. Sex therapy, **reconstructive surgery**, or altering habits so that sexual needs are met without intercourse all may be options after surgery that radically affects the genitals.

Another common effect of cancer treatment is premature menopause. This may follow removal of ovaries by surgery, suppression of ovaries by chemotherapy or radiation therapy of the pelvis. The symptoms are much more severe than normal menopause causing vaginal dryness and tightness, hot flashes and sometimes low androgen levels which can also reduce sexual desire. Women who do not have hormone-sensitive tumors may want to consider hormone replacement therapy, after consultation with their doctor. Radiation treatment of the pelvis, cervix or vagina may cause scarring of the vagina. This makes it tighter and difficult to penetrate. Series of vaginal dilators of different sizes can help to relieve this problem. It is important to use these early to prevent vaginal shrinkage. Counseling may also be beneficial for the affected woman and her partner.

Cancer and male sexuality

Radiation therapy of the pelvis can impair sexual function. Circulating **testosterone** levels may come down temporarily and during this time men may have a loss of sexual desire. But this does not seem to be a permanent effect in all cases. It may be possible to get aroused by taking more time and experimenting with different kinds of caressing and love making. If erection does not occur after a significant period of time the doctor may suggest tests to check for sleep erections. Some are take-home tests and if they suggest that erection occurs normally during sleep, it is clear the physiological mechanism is intact and sexual counseling may relieve the problem. Sexual counseling may also be helpful to allow enjoyment with sexual caressing in the absence of erections. Men with medical impotence may also be helped by the use of Viagra. Men need replacement with hormones in only very rare cases. In fact, extra testosterone can cause undetected **prostate cancer** to grow.

Surgery for various cancers can cause sexual problems. Surgery for **bladder cancer** can lead to decreased sexual desire, lowered ability to obtain an erection, and less frequent or less intense orgasms. Surgery for **penile cancer** and **testicular cancer** can result in decreased fertility and desire, difficulties with erections and orgasms, and decreased volume of semen. In treating prostate cancer, the **biopsy** obtained to confirm diagnosis may decrease semen levels, and, after a man has had his prostate gland removed (**prostatectomy**), he may be unable to obtain an erection. However, new surgical advances and new chemotherapy options may help reduce these effects.

If, during surgery, the blood supply to the penis is affected, the surgeon may take an abdominal artery and try to connect it the penis. This operation is only successful in a quarter of the patients. Penile injection therapy and vacuum devices have been used to produce erections in the absence of sufficient blood flow. Medications that produce erections are risky and may lead to the formation of scar tissue. Vacuum erection devices are safer but intrude in the lovemaking. Medical erection problems

may also be treated by penile prosthesis. This is one of the best ways to treat a permanent erection problem.

Sexual problems of specific cancer treatments

Urostomy or colostomy

Before sexual activity one must ensure that the **urostomy** fits correctly. The appliance should be emptied to reduce the chance of a leak. A patterned pouch can be worn over it to cover it. Sexual activity with a **colostomy** can be performed with the same precautions. One can plan sexual activity at a time when the colostomy is not active and avoid gas-producing foods that day. Direct communication and reassurances from a loving partner can be extremely helpful.

Mastectomy

The breast symbolizes sexuality and when the treatment of **breast cancer** involves **mastectomy**, psychological counseling is helpful to regain desire and sexual enjoyment. There may be fewer problems when a **lumpectomy** is done. Women who feel awkward about the change after surgery may consider using a prosthesis covered with a nightgown or bra, or they may consider reconstruction either with or without implantation.

Limb amputation

Treatment mainly of primary tumors of bone often includes amputating a limb. If the partners can openly communicate they can decide whether the prosthesis needs to be worn during lovemaking. Prosthesis can help with movement and balance but the straps that attach it can get in the way. If the prosthesis is not used, pillows could be used instead for balance.

Treatment of facial cancer

Some cancers of the head and neck may be treated by partial removal of the facial bony structure. This can be psychologically very damaging as the scar is so public and affects the face, a vital part of the human personality. Following such surgery, speech may also be affected. Recent advances in facial prosthesis and plastic surgery may help regain a more natural appearance and speech.

Professional help for sexual problems

The first step is to discuss sexual problems with one's doctor. Sometimes doctors themselves may not be at ease discussing sexual issues. Cancer centers may have sexual rehabilitation centers with experts on staff comfortable dealing with these issues. Medical schools and some private practice groups run sexual dysfunction clinics that provide comprehensive care to treat sexual problems. Sex therapists can provide sexual counseling. It is important that the sex therapist be a psychiatrist, social worker or psychologist with special training in treating sexual problems. Professional societies such as American Association for Marriage and Family Therapy can give information about these specialists. It is important to avoid untrained people who provide useless and sometimes harmful therapy.

See also Body image; Fertility issues.

Resources

ORGANIZATIONS

The American Association for Marriage and Family Therapy. 1133 15th Street NW, Suite 300, Washington D.C. 20005. Telephone: (202) 452-0109 Web site: <http://www.aamft.org>.

American Cancer Society. Telephone: 1-800-ACS-2345. Web site: <http://www.cancer.org>.

OTHER

The American Cancer Society. *Sexuality and Cancer: For the Man Who Has Cancer and His Partner*. *Sexuality and Cancer: For the Woman Who Has Cancer and Her Partner*. Other publications also available free from the American Cancer Society. Telephone: 1-800-ACS-2345. Also available through the web site: <http://www.cancer.org>.

"For Women:Body Image Issues." *Gillette Women's Cancer Connection*. <http://www.gillettecancerconnect.org>.

Malini Vashishtha, Ph.D.

Sézary syndrome

Definition

Sézary syndrome is a type of **cutaneous T-cell lymphoma**, characterized by skin abnormalities, extreme **itching**, enlarged lymph glands, and abnormal blood cells.

Description

Sézary syndrome is a type of lymphoma, which is a disease where lymphocytes (a type of white blood cell) increase to very large numbers in a person's blood. Sézary syndrome is a type of lymphoma known as a cutaneous T-cell lymphoma, meaning that it is a disease where

the white blood cells known as T-lymphocytes increase to large numbers.

Sézary syndrome can affect many organs. In early stage disease, the skin is the only organ affected; however, later stage disease can affect other organ systems.

Demographics

Sézary syndrome is relatively rare, affecting about one in one million people. The incidence of the syndrome increases with age, with most cases appearing in people in their 50s or 60s. Men appear to be affected more often than women, and black males appear to be at higher risk of developing the syndrome than white males.

Causes and symptoms

There are no known causes of Sézary syndrome. Early in the course of study of the syndrome, it was thought that exposure to certain chemicals could trigger the disease. However, later studies have not shown any relation between industrial chemical exposure and Sézary syndrome

The symptoms of Sézary syndrome can be very subtle; because of this, it is often not diagnosed for many years. Early symptoms include skin lesions that can look like eczema and psoriasis. Later symptoms can include skin tumors, especially in body folds. Enlarged lymph glands in the neck, armpits, and groin can accompany the skin tumors. Later in the course of Sézary syndrome symptoms may relate to other areas of disease involvement.

Diagnosis

The diagnosis of Sézary syndrome is made by careful clinical evaluation. Generally, a patient with Sézary syndrome seeks treatment for skin lesions that are not responsive to ordinary medications. If the doctor suspects a cutaneous T-cell lymphoma, a blood test is ordered to see if there are any abnormalities, such as an increase or decrease in lymphocytes and the presence or absence of Sézary cells, which are certain white blood cells with a distinctive shape when viewed under a microscope. Finally, a sample (**biopsy**) of one the skin lesions is done to see if the lesion is part of Sézary syndrome or caused by some other disease.

Clinical staging, treatment, prognosis

Staging for cutaneous T-cell lymphoma, including Sézary syndrome, is based on the extent of skin involvement and the presence or absence of other manifestations of the syndrome. Stage I is characterized by mild skin involvement. In stage II there is extensive skin involvement, including skin tumors. Patients in stage III and IV have extensive skin involvement, blood abnormalities including Sézary cells, and swollen lymph nodes.

There are multiple therapies for Sézary syndrome. However, unless the disease is in an early stage, the chances for a complete cure are small. Nonspecific treatment includes skin lubricants and moisturizers to help treat the skin irritation and dryness that is common with the syndrome. Low potency steroid creams or ointments may be used to help treat itching and skin inflammation.

The first therapy used with some success against Sézary syndrome is mechlorethamine, or nitrogen mustard. It is applied daily to the entire skin surface (except for sensitive areas such as eyelids and genitalia) for six to twelve months, then three times a week for one to two years more. Several studies have investiagted the effectiveness of nitrogen mustard therapy, and have found that in stage I or II disease, the therapy causes complete remission in 60–80% of patients. Side effects are minimal, but dry skin, irritation, and change in skin pigmentation can occur.

Another treatment that has been used for many years, especially for stage II and III disease, is electron beam **radiation therapy**. Treatment with electron beam radiation therapy has been used since 1953, with good response rates seen in 50–70% of patients. Side effects can include excessive skin dryness, skin blistering, loss of hair on treated areas, and increased risk of skin cancer.

ECP, or photophoresis, has been approved by the FDA as a treatment for Sézary syndrome. In this mode of treatment, phototherapy with ultraviolet light is combined with leukapheresis. In leukapheresis, a person's blood is taken out and passed through special filters that remove circulating Sézary cells; the cells are treated with ultraviolet radiation, then reinfused into the patient. Response rates range from 55% to 75%, with some reports showing a 15–25% cure rate. Side effects can include nausea and **fever**.

Systemic **chemotherapy** is often used in patients who are in later stages of the disease. Using standard cancer chemotherapeutic agents such as **cyclophosphamide**, **vincristine**, and **doxorubicin**, response rates up to 19 months have been seen. No studies have shown an increased survival rate in patients getting aggressive, high-dose chemotherapy versus those getting more standard doses.

The prognosis for patients with Sézary syndrome is based on placing the patient in one of three categories:

KEY TERMS

Eczema—A superficial inflammation of the skin, generally with itching and a red rash.

Psoriasis—A chronic skin condition, causing red, scaling patches to appear to the skin.

Interferon —A substance produced by cells that can enhance the immune system.

Monoclonal antibodies —Antibodies made in the lab that can identify and target specific infectious agents and cancers.

good, intermediate, or poor. Patients with good prognosis have the condition limited to their skin. Their general survival time is more than 10 years. Patients in the intermediate category have skin lesions including tumors and plaques, but no blood involvement. Their survival time is five years. Patients in the poor risk category have extensive skin lesions along with blood abnormalities, including high levels of Sézary cells. Patients in this category, even with extensive treatment, generally have survival rates of only one year or less.

Coping with cancer treatment

There are multiple ways to help patients cope with side effects brought about by the treatment of Sézary syndrome. Lubricants can be used to help dryness, scaling, and itching of the skin caused by the use of topical treatments such as nitrogen mustard and electron beam therapy. Symptoms such as **nausea and vomiting**, caused by ECP and systemic chemotherapy, can be treated with standard anti-nausea and vomiting medication.

Clinical trials

In 2001, **clinical trials** are underway to investigate several forms of innovative treatment for cutaneous T-cell lymphoma and Sézary syndrome. Interferon has been used with some success in both early and late stage disease. Common side effects include a decrease in white blood cells and chronic **fatigue**. The use of **monoclonal antibodies** in treating late stage disease (III and IV) has been recently studied. Early studies have shown response rates of around 30%. Side effects include allergies to the monoclonal antibodies, fever, and fatigue.

Prevention

As of 2001, there are no known ways to prevent Sézary syndrome.

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Edward R Rosick, D.O., M.P.H., M.S.

Shingles *see* **Herpes zoster**

Shunt *see* **Peritoneovenous shunt**

Sigmoidoscopy

Definition

Sigmoidoscopy is a procedure by which a doctor inserts either a short and rigid or slightly longer and flexible fiber-optic tube into the rectum to examine the lower portion of the large intestine (or bowel).

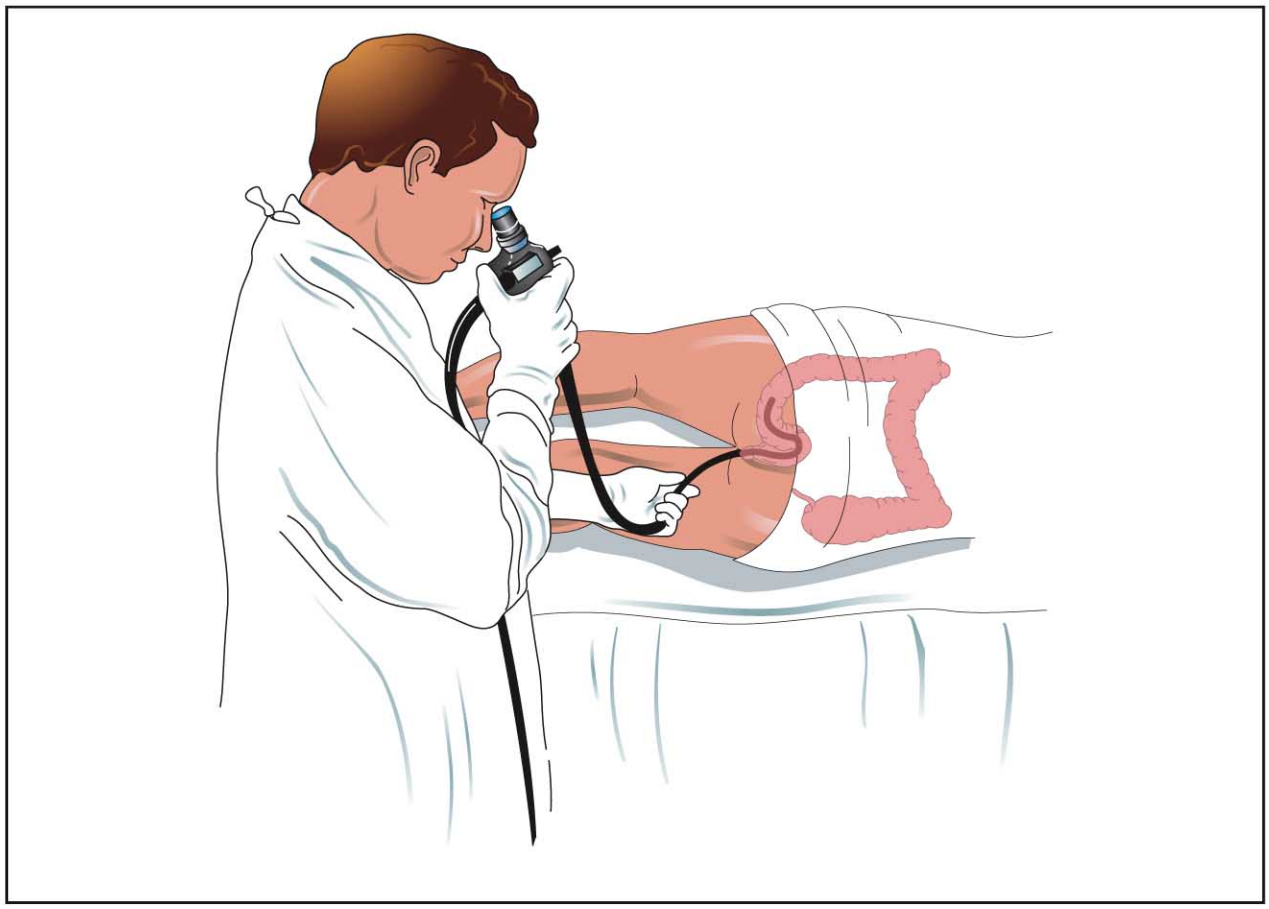
Purpose

Sigmoidoscopy is used most often in screening for colorectal cancer or to determine the cause of rectal bleeding. It is also used for the diagnosis of inflammatory bowel disease and other benign diseases of the lower intestine.

Cancer of the rectum and colon is the second most common cancer in the United States, claiming the lives of about 56,000 people annually. As a result, The American Cancer Society recommends that people age 50 and over be screened for colorectal cancer every five years. The screening includes a flexible sigmoidoscopy. Screening at an earlier age should be done on patients who have a family history of colon or **rectal cancer**, or small growths in the colon (polyps).

Individuals with inflammatory bowel disease (Crohn's colitis or ulcerative colitis) are at increased risk for colorectal cancer and should begin their screenings at a younger age, and be screened more frequently. Many doctors screen such patients more often than every three to five years. Those with ulcerative colitis should be screened beginning 10 years after the onset of disease; those with Crohn's colitis beginning 15 years after the onset of disease.

Some doctors prefer to do this screening with a colonoscope, which allows them to see the entire colon (cer-



Sigmoidoscopy is a procedure most often used in screening for colorectal cancer and as a test in diagnosis of possible inflammatory bowel disease. As illustrated above, the physician can view the rectum and colon through a sigmoidoscope, a flexible fiber-optic tube which contains a light source and a lens. *(Illustration by Electronic Illustrators Group.)*

tain patients, such as those with Crohn's colitis or ulcerative colitis, must be screened with a colonoscope). However, compared with sigmoidoscopy, **colonoscopy** is a longer process, causes more discomfort, and is more costly.

Studies have indicated that about one-fourth of all precancerous or small cancerous growths in the colorectal region can be seen with a rigid sigmoidoscope. The longer, flexible version, which is the primary type of sigmoidoscope used in the screening process, can detect more than one-half of all growths in this region. This examination is usually performed in combination with a **fecal occult blood test**, in an effort to increase detection of polyps and cancers that lie beyond the scope's reach.

Precautions

The exam is not always adequate. A 2004 study reported that among older patients and women, sigmoidoscopy is not always effective, particularly because insertion depth is not adequate. For unknown reasons, this is almost twice as true for women as for men.

Sigmoidoscopy can usually be conducted in a doctor's office or a health clinic. However, some individuals should have the procedure done in a hospital day surgery facility. These include patients with rectal bleeding, and patients whose blood does not clot well (possibly as a result of blood-thinning medications).

Description

Most sigmoidoscopy is done with a flexible fiber-optic tube. The tube contains a light source and a camera lens. The doctor moves the sigmoidoscope up beyond the rectum (the first 1 ft/30 cm of the colon), examining the interior walls of the rectum. If a 2 ft/60 cm scope is used, the next portion of the colon can also be examined for any irregularities.

The procedure takes 20 to 30 minutes, during which time the patient will remain awake. Light sedation may be given to some patients. There is some discomfort (usually bloating and cramping) because air is injected into the bowel to widen the passage for the sigmoidoscope. Pain is rare except in individuals with active inflammatory bowel disease.

In a colorectal cancer screening, the doctor is looking for polyps or tumors. Studies have shown that over time, many polyps develop into cancerous lesions and tumors. Using instruments threaded through the fiber-optic tube, cancerous or precancerous polyps can either be removed or biopsied during the sigmoidoscopy. People who have cancerous polyps removed can be referred for full colonoscopy, or more frequent sigmoidoscopy, as necessary.

The doctor may also look for signs of ulcerative colitis, which include a loss of blood flow to the lining of the bowel, a thickening of the lining, and sometimes a discharge of blood and pus mixed with stool. The doctor can also look for Crohn's disease, which often appears as shallow or deep ulcerations, or erosions and fissures in the lining of the colon. In many cases, these signs appear in the first few centimeters of the colon above the rectum, and it is not necessary to do a full colonoscopic exam.

Private insurance plans often cover the cost of sigmoidoscopy for screening in healthy individuals over 50, or for diagnostic purposes. Medicare covers the cost for diagnostic exams, and may cover the costs for screening exams.

Preparation

The purpose of preparation for sigmoidoscopy is to clean the lower bowel of stool so that the doctor can see the lining. Many patients are required to consume only clear liquids on the day before the test, and to take two enemas on the morning of the procedure. The bowel is cleaner, however, if patients also take an oral laxative preparation of 1.5 oz phospho-soda the evening before the sigmoidoscopy.

Certain medications should be avoided for a week before having a sigmoidoscopy. These include:

- apirin, or products containing aspirin
- ibuprofen products (Nuprin, Advil, or Motrin)
- iron or **vitamins** containing ironAlthough most prescription medication can be taken as usual, patients should check with their doctor in advance.

Aftercare

Patients may feel mild cramping after the procedure that will improve after passing gas. Patients can resume their normal activities almost immediately.

KEY TERMS

Biopsy—A procedure where a piece of tissue is removed from a patient for diagnostic testing.

Colorectal cancer—Cancer of the large intestine, or colon and rectum (the last 16 inches of the large intestine before the anus).

Inflammatory bowel disease—Ulcerative colitis or Crohn's colitis; chronic conditions characterized by periods of diarrhea, bloating, abdominal cramps, and pain, sometimes accompanied by weight loss and malnutrition because of the inability to absorb nutrients.

Polyp—A small growth that can be precancerous when it appears in the colon.

Risks

There is a slight risk of bleeding from the procedure. This risk is heightened in individuals whose blood does not clot well, either due to disease or medication, and in those with active inflammatory bowel disease. The most serious complication of sigmoidoscopy is bowel perforation (tear). This complication is very rare, however, occurring only about once in every 7,500 procedures.

Normal results

A normal exam shows a smooth bowel wall with no evidence of inflammation, polyps or tumors.

Abnormal results

For a cancer screening sigmoidoscopy, an abnormal result involves one or more noncancerous or precancerous polyps or tumors. Patients showing polyps have an increased risk of developing colorectal cancer in the future.

Small polyps can be completely removed. Larger polyps or tumors usually require the doctor to remove a portion of the growth for diagnostic testing. Depending on the test results, the patient is then scheduled to have the growth removed surgically, either as an urgent matter if it is cancerous, or as an elective surgery within a few months if it is noncancerous.

In a diagnostic sigmoidoscopy, an abnormal result shows signs of active inflammatory bowel disease, either a thickening of the intestinal lining consistent with ulcerative colitis, or ulcerations or fissures consistent with Crohn's disease.

QUESTIONS TO ASK THE DOCTOR

- Why do I need a sigmoidoscopy?
- Should I undergo a colonoscopy instead?
- If a biopsy is done, how long before I get the results?
- Will I need to have this test again in the future? When?

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Sirolimus

Definition

Sirolimus is indicated by the Food and Drug Administration (FDA) to be used after a kidney transplant to prevent the body from rejecting the new kidney. Sirolimus may also have a role in prevention of organ rejection in heart or lung transplantation, and prevention of graft-versus-host disease in patients undergoing **bone marrow transplantation**. Sirolimus (formerly known as rapamycin) became available at the end of 1999 and is marketed under the brand name Rapamune by Wyeth-Ayerst Laboratories.

Description

Sirolimus belongs to a class of macrolide **antibiotics** and is isolated from an organism named *streptomyces hygriscopicus*.

Sirolimus prevents the immune system from attacking the transplanted organ by decreasing the growth of certain chemicals in the body responsible for the immune function (B and T lymphocytes). Sirolimus works differently from other immunosuppressants used to prevent organ rejection after transplantation (**azathioprine**, mycophenolate mofetil, **tacrolimus**, cyclosporine, and steroids). It should be given in combination with cyclosporine and steroids to prevent acute rejection of a transplanted kidney. This drug is available as a tablet and a liquid and can be used in children and adults.

Recommended dosage

Adults

KIDNEY TRANSPLANTATION The first dose of 3 tablets (2 mg each) or 6 milliliters of oral solution should be given as soon as possible after a kidney is transplanted. Then, a maintenance dose of 2 mg should be given once a day.

Children over 13 years of age and Adults less than 40 kg (88 lbs)

KIDNEY TRANSPLANTATION 3 mg of sirolimus per square meter of body surface area on day 1 after transplantation, followed by a maintenance dose of 1 mg per square meter per day.

Children less than 13 years of age

Check with a physician.

Administration

Sirolimus should be administered in combination with cyclosporine and steroids. To decrease the risk of side effects, sirolimus should be given four hours after cyclosporine. To avoid variations in blood levels, sirolimus should be taken consistently— either always with food or always without food. Sirolimus oral solution should only be mixed with water or orange juice and consumed immediately. Juices or liquids other than water or orange juice should not be used to mix sirolimus. Bottled sirolimus solution should be stored in the refrigerator, but not frozen. Refrigerated sirolimus solution may develop a slight haze. If haze is noticed, the drug should be left at room temperature and gently shaken until haze disappears. If a dose is missed, it should taken as soon as possible unless it is almost time for the next dose. Two doses at the same time should not be taken.

Precautions

Sirolimus may increase the risk of the following conditions:

KEY TERMS

Immune system—The body's mechanism to fight infections, toxic substances, and to recognize and neutralize or eliminate foreign material (for example, a body organ transplanted from another person).

Immunosuppressant—An agent that decreases activity of immune system (for example, radiation or drugs).

Lymphocele—A mass surrounded by an abnormal sac that contains lymph (fluid that is collected from tissues throughout the body) from diseased or injured lymphatic channels.

Lymphoma—Any malignant (cancerous) disorder of lymphoid tissue.

Steroids—Drugs such as prednisone or dexamethasone, which resemble body's natural hormones and are often used to decrease inflammation or to suppress activity of immune system.

Transplant—Tissue transferred from one part of the body to another or from one person to another.

- infections caused by viruses and bacteria
- lymphoma or skin cancer
- elevated blood lipids (cholesterol and triglycerides)
- decreased kidney function
- lymphocele formation after a kidney transplantation

Patients with the following conditions should use sirolimus with caution:

- an allergic reaction to tacrolimus (has a similar structure to sirolimus)
- liver disease (dose of sirolimus may need to be decreased)
- treatment with medications that are broken down in the liver and that may interact with sirolimus
- Pregnancy. These patients should use an effective method of birth control started before therapy with sirolimus and continued for 12 weeks after stopping this medication.

Patients should immediately alert their doctor if any of these symptoms develop:

- fever, chills, sore throat
- fast heartbeat
- trouble breathing
- unusual bleeding or bruising

Sirolimus should be taken consistently with regard to meals (either always taken with food or always taken on an empty stomach) and at least four hours after cyclosporine to decrease variability of blood sirolimus levels. Patients should avoid grapefruit or grapefruit juice because it may increase sirolimus levels in the blood. Those taking sirolimus will need to see a physician regularly to check blood and urine.

Side effects

The most common side effects include mild dose-related risk of bleeding, elevated blood cholesterol and triglyceride values, decreased kidney function, high blood pressure, **diarrhea** or constipation, rash, acne, joint pain, nausea, vomiting, stomachache, and decreased blood potassium and phosphate values. Sirolimus can decrease the number of red blood cells, which can cause a patient to look pale, feel tired, short of breath, and drowsy, and experience heart palpitations. People who are allergic to tacrolimus may develop an allergy when taking sirolimus.

Interactions

Sirolimus is broken down in the liver by the same enzyme system that also breaks down cyclosporine and tacrolimus. Because cyclosporine can increase sirolimus blood levels, sirolimus should be given four hours after the morning cyclosporine dose to decrease the risk of side effects. Diltiazem (Cardizem, Tiazac, Dilacor) and ketoconazole (Nizoral) can increase sirolimus blood levels. The use of ketoconazole should be avoided in patients taking sirolimus. Other drugs that are likely to increase sirolimus blood levels and increase its side effects include calcium channel blockers (used to treat high blood pressure), drugs that treat fungal infections (ketoconazole, itraconazole, fluconazole), macrolide antibiotics (erythromycin, clarithromycin), and anti-HIV drugs (ritonavir, nelfinavir, indinavir). Rifampin can greatly decrease sirolimus blood levels, potentially making it less effective. Other drugs that may decrease effectiveness of sirolimus include phenobarbital, **carbamazepine**, rifabutin, and **phenytoin**. Anyone who is taking these drugs should ask their physician if they could safely take sirolimus.

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Sjögren's syndrome

Description

Sjögren's syndrome (SS) is an autoimmune disease, which means that the immune system has mounted an

attack against specific tissues of the body. For example, most patients with Sjögren's syndrome carry antibodies to molecules found in the nucleus of cells (antinuclear antibodies). Although Sjögren's syndrome can affect practically any organ in the body, it is characterized by dry mouth (**xerostomia**) and dry eyes (xerophthalmia). These hallmark symptoms are known as "sicca symptoms." Sjögren's syndrome goes by many names which include Sjögren's disease, dry-mouth and dry-eyes disease, sicca complex, and sicca syndrome. The disorder is named for Henrik Sjögren, a Swedish ophthalmologist.

Symptoms of Sjögren's syndrome include dry mouth, difficulty or inability to swallow (dysphagia), tooth decay (dental caries), impaired taste and smell, dry eyes, eye pain, eye redness, muscle pain (myalgia), and **fatigue**. Many patients develop a variety of skin problems that include dry patches, vasculitis, and cutaneous B-cell lymphoma. Other less common symptoms include **diarrhea**, headaches, joint pain (arthralgia), muscle weakness, hair loss (alopecia), and dry cough. About 33% of patients develop arthritis. Patients with cancer of lymphoid tissue (lymphoma) and Sjögren's syndrome have **fever**, nerve involvement, low numbers of red blood cells (**anemia**) and white blood cells (lymphopenia), inflammation of blood vessels of the skin (skin vasculitis), and disease of the lymph nodes (lymphadenopathy) much more frequently than patients with Sjögren's syndrome alone.

The symptoms of Sjögren's syndrome can have a pronounced effect on quality of life. Besides causing discomfort, the symptoms also disrupt sleep, which can have side effects such as fatigue, difficulty concentrating, and **depression**. Patients with Sjögren's syndrome are at risk for tooth decay and yeast infections in the mouth (erythematous candidiasis). Approximately 5% of the patients with Sjögren's syndrome develop malignant lymphoma.

SS is found in all races and ethnic groups. It is thought to affect between 0.1% and 3% of the population in the United States; this range reflects the lack of a uniform set of diagnostic criteria. According to the American College of Rheumatology, between 1 million and 4 million Americans have Sjögren's syndrome.

Causes

The cause of Sjögren's syndrome is unknown, although several viruses are suspected triggers of the autoimmune reaction. In 2004 a team of researchers in Greece presented evidence that a coxsackievirus may be the cause of SS. The sicca symptoms of Sjögren's syndrome are caused by the invasion and multiplication of white blood cells (lymphocytes) into the salivary glands and tear glands. The lymphocytes destroy the gland tissue and cause the glands to malfunction, reducing the production of tears and saliva. This invasion by lymphocytes, however, does not fully account for the sicca symptoms. Other, as yet unidentified, factors play a role in the development of the sicca symptoms.

Sjögren's syndrome can occur in combination with certain cancers. For more than half of the patients with non-Hodgkin lymphoma, the lymphoma is located in the salivary glands, causing them to malfunction. **Graft-vs.-host disease** in patients who have undergone **bone marrow transplantation** can cause eye problems similar to those seen in Sjögren's syndrome. Both **chemotherapy** and **radiation therapy** to the head and neck can cause xerostomia.

Treatments

There is no cure for Sjögren's syndrome. Therefore, treatment is aimed at relieving symptoms. Dry eyes may be treated with eye drops and avoidance of drying conditions such as wind, hair dryers, and medications that cause dry eyes (e.g. tricyclic antidepressants). Eyeglasses may protect the eyes from wind. The lower tear ducts may be blocked with silicone plugs (punctal occlusion) to conserve natural tears. Use of humidifiers, both at home and at work, can significantly reduce sicca symptoms. Saliva substitutes and sugar-free hard candies or chewing gum, which stimulate salivation, can reduce sicca symptoms. The drugs **pilocarpine** (Salagen) and cevimeline (Evoxac) can increase salivation. Cevimeline also has been found effective in relieving the symptom of dry eye in SS as well. Pain may be relieved by nonsteroidal anti- inflammatory drugs (e.g. Aleve) or other pain medications.

The patient with Sjögren's syndrome should faithfully conduct routine daily oral hygiene consisting of tooth brushing two to three times, flossing once, and utilizing medicated rinses as prescribed by the physician. Fluoride varnishes applied by a dentist and nightly fluoride treatments can help to prevent dental caries. Brushing and flossing should be performed carefully to prevent damage to the weakened oral mucosa.

Alternative and complementary therapies

In a controlled clinical study, the herbal vitamin supplement LongoVital was shown to increase the rate of salivation. Sicca symptoms may be reduced by acupuncture. Papayas contain papain, which is an enzyme that breaks up proteins. Eating papayas, drinking papaya juice, or drinking a solution of crushed papain tablets in water can liquefy thick saliva. Drinking a solution of meat tenderizer (which contains papain) in water is another alternative.

KEY TERMS

Autoimmune disease—A disease caused by the abnormal presence of antibodies against normal tissues of the body.

Coxsackievirus—Any of a group of enteroviruses that produce a disease in humans characterized by fever and rash. Coxsackieviruses are named for the town in upstate New York where they were first identified.

Lymphocytes—White blood cells. Lymphocytes play a vital role in the immune system.

Lymphoma—Any cancer of the tissues that make up the lymphatic system.

Sicca symptoms—Dry mouth and eyes.

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ORGANIZATIONS

American College of Rheumatology. 1800 Century Place, Suite 250, Atlanta, GA 30345-4300. (404) 633-3777. Fax: (404) 633-1870. <http://www.rheumatology.org>.

Sjögren's Syndrome Foundation, Inc. 8120 Woodmont Avenue, Bethesda, MD 20814. (800) 475-6473. Fax: (301) 718-0322.<http://www.sjogrens.org>.

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Skin cancer *see* **individual cancers: Basal cell carcinoma; Bowen's disease; Melanoma; Merkel cell carcinoma; Squamous cell carcinoma, Trichilemmal carcinoma**

Small intestine cancer

Definition

Cancer of the small intestine is a rare disease that results when abnormal, malignant cells divide out of control. Cancers in this location consist primarily of adenocarcinoma, **lymphoma**, sarcoma, and carcinoid tumors.

Description

The small intestine is a long tube inside the abdomen divided into three sections: the duodenum, jejunum, and ileum. The function of the small intestine is to break down food and to remove proteins, carbohydrates, fats, **vitamins**, and minerals. Obstruction of the small intestine by cancer may impair normal passage and digestion of food and nutrients.

Adenocarcinoma

These malignancies most often start in the lining of the small intestine, most frequently occurring in the duodenum and jejunum, the sections closest to the stomach. These tumors may obstruct the bowel, causing digestive problems. Adenocarcinoma is the most common cancer of the small intestine, but only accounts for 2% of all tumors in the gastrointestinal tract and 1% of all deaths related to cancer of the gastrointestinal tract. Carcinomas of the small intestine may appear at multiple sites.

Lymphoma

This fairly uncommon cancer is typically a non-Hodgkin's type that starts in the lymph tissue of the small intestine. (The body's immune system is comprised of lymph tissue, which assists in fighting infections.) Malignant lymphoma is not often found as a solitary lesion.

Sarcoma

Sarcoma malignancies of the small intestine are usually **leiomyosarcoma**. They most often occur in the smooth muscle lining of the ileum, the last section of the small intestine. Liposarcoma and angiosarcoma occur more rarely in the small intestine.

Carcinoid tumors

Carcinoid tumors are most often found in the ileum. In approximately 50% of cases, they appear in multiples.

Demographics

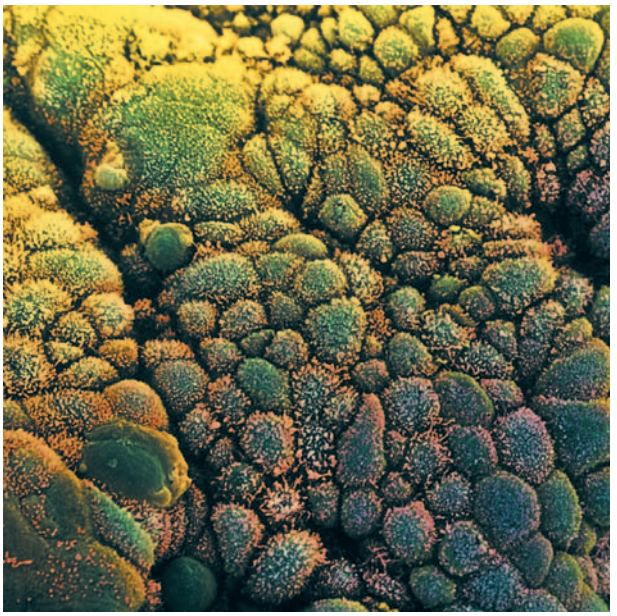
Approximately 50% of small intestine cancers are adneocarcinomas; 20% are lymphomas; 20% are carcinoid; and about 10% are **sarcomas**.

Causes and symptoms

The causes of this cancer are not known, but factors that contribute to its development include exposure to carcinogens such as chemicals, radiation, and viruses. In addition, smoking and a poor diet may contribute to the incidence of small intestine cancer. The incidence of cancer is higher in obese individuals.

Often cancer of the small intestine does not initially produce any symptoms. Gastrointestinal bleeding is perhaps the most common symptom. A doctor should be consulted if any of these symptoms are present:

- involuntary **weight loss**
- a lump in the abdominal region
- blood in the stool
- pain or cramping in the abdominal region



Colored scanning electron micrograph (SEM) of cancer cells in the intestine. *(Copyright Quest, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Diagnosis

Evaluation begins by taking a patient's medical history and conducting a physical examination. If a patient experiences symptoms, a doctor may suggest the following tests:

- Upper gastrointestinal x ray/upper GI series: To allow the stomach to be seen easier on an **x ray**, the patient drinks a liquid called barium. This test can be conducted in either a doctor's office or a radiology department at a hospital.
- CT scan (computed tomography): A computerized x ray that takes a picture of the abdomen.
- MRI scan (**magnetic resonance imaging**): A imaging technique that uses magnetic waves to take a picture of the abdomen.
- Ultrasound: An imaging technique that uses sound waves to locate tumors.
- Endoscopy: An endoscope is a thin, lighted tube which is placed down the throat to reach the first section of the small intestine (duodenum). During this procedure, the doctor may take a **biopsy**, in which a small piece of tissue is removed for examination of cancereous cells under a microscope.

If small intestine cancer is evident, more tests will be conducted to determine if cancer has spread to other parts of the body.

Treatment team

Cancer treatment often requires a team of specialists and may include a surgeon, medical oncologist, radiation oncologist, nurse, physical therapist, occupational therapist, dietitian, and or a social worker.

Clinical staging, treatments, and prognosis

As with many other types of cancer, malignancies of the small intestine can be classified as localized, regional spread, or distant spread.

- Localized: The cancer has not spread beyond the wall of the organ it developed in.
- Regional spread: The cancer has spread from the organ it started in to other tissues such as muscle, fat, ligaments, or lymph nodes.
- Distant spread: The cancer has spread to tissues or organs outside of where it originated such as the liver, bones, or lungs.

Treatment options for small intestine cancer most often include surgery, and possibly **radiation therapy**, **chemotherapy**, and/or biological therapy. Cancer of the small intestine is treatable and sometimes curable depending on the histology. Removing the cancer through surgery is the most common treatment. If the tumor is large, a small portion may be removed if resection of the small intestine is possible. For larger tumors, surgery requires removing a greater amount of the surrounding normal intestinal tissue, in addition to some surrounding blood vessels and lymph nodes.

Radiation therapy kills cancer cells and reduces the size of tumors through the use of high-energy x rays. Radiation therapy may come from an external source using a machine or an internal source. Internal-based therapy involves the use of radioisotopes to administer radiation through thin plastic tubes to the area of the body where cancer cells are found. Side effects of radiation therapy include:

- fatigue
- loss of appetite
- nausea and vomiting
- **diarrhea**
- gas
- bloating
- mild temporary, sunburn-like skin changes
- difficulty tolerating milk products

Chemotherapy kills cancer cells with drugs taken orally or by injection in a vein or muscle. It is referred to as a systemic treatment due to fact that it travels through the bloodstream and kills cancer cells outside the small intestine. Adjuvant chemotherapy may be given following surgery to ensure all cancer cells are killed. Some side effects of chemotherapy are:

- nausea and vomiting
- loss of appetite (anorexia)
- temporary hair loss (alopecia)
- mouth sores
- fatigue, as a result of a low red blood cell count
- higher likelihood of infection or bleeding due to low white blood cell counts and low blood platelets, respectively

Radiation and chemotherapy are seldom beneficial in small intestinal cancers.

Utilizing the body's immune system, biological therapy stimulates the body to combat cancer. Natural materials from the body or other laboratory-produced agents are designed to boost, guide, or restore the body's ability to fight disease.

Treatment options for small interstine cancers are based on the type of cells found—adenocarcinoma, lymphoma, sarcoma, or carcinoid tumor—rather than the clinical staging system.

Treatment of adenocarcinoma of the small intestine may consist of:

- surgical removal of the tumor
- If the cancer cannot be removed by resection of the small intestine, surgery may be performed to bypass the cancer to allow food to travel through the intestine.
- symptom relief with radiation therapy
- chemotherapy or biological therapy in a clinical trial setting
- a clinical trial involving radiation and drug therapy (with or without chemotherapy) to elicit greater sensitivity to radiation using radiosensitizers

Treatment of lymphoma of the small intestine may consist of:

- surgical removal of the cancer and lymph nodes in close proximity to it
- Surgery accompanied by radiation therapy or adjuvant chemotherapy. If the disease is localized to the bowel wall, then surgical resection alone or combined chemotherapy should be considered. If the disease has extended to the regional lymph nodes, then surgical resection and combination chemotherapy is suggested at the time of diagnosis.

- For extensive lymphoma or lymphoma that cannot be removed surgically, chemotherapy with or without additional radiation therapy is frequently used to reduce the risk of recurrence.

Treatment of leiomyosarcoma of the small intestine may consist of:

- surgical removal of the cancer
- When cancer cannot be removed by resection, surgical bypass of the tumor is recommended to allow food to pass.
- radiation therapy
- For unresectable metastatic disease, surgery, radiation therapy, or chemotherapy is suggested in order to alleviate symptoms.
- For unresectable primary or metastatic disease, a clinical trial evaluating the benefits of new anticancer drugs (chemotherapy) and biological therapy.

For recurrent small intestine cancer, treatment may consist of the following measures, if the cancer has returned to one area of the body only:

- surgical removal of the cancer
- symptom relief using chemotherapy or radiation therapy
- a clinical trial using radiation and drug therapy (with or without chemotherapy) to elicit greater sensitivity to radiation using radiosensitizers

For recurrent metastatic adenocarcinoma or leiomyosarcoma, there is no standard effective chemotherapy treatment. Patients should be regarded as candidates for clinical studies assessing new anticancer drugs or biological agents.

For carcinoid tumors at least than 1 cm in size, surgical removal of the tumor and surrounding tissue is possible. Carcinoid tumors often grow and spread slowly, therefore, approximately half are found at an early or localized stage. By the time of sugery, 80% of the tumors over 2 cm in diameter have metastasized locally or to the liver.

The prognosis or likelihood of recovery depends on the type of cancer, the overall health of the patient, and whether the cancer has spread to other regions or is only localized in the small intestine. A cure depends on the ability to remove the cancer completely with surgery. Adenocarcinoma is most common in the duodenum, however, patient survival is less likely for individuals with cancer is in this area compared with those patients with tumors in the jejunum or ileum due to reduced rates of surgery to remove cancer. Between 1985-1995, there were 4,995 cases of adenocarcinoma of the small intestine reported to the National Cancer Database. Of these malignancies, 55% occurred in the duodenum, 13% in the ileum, 18% in the jejunum, and 14% were in unspecified areas. The National Cancer Database reported a median survival of 19.7 months for these patients with an overall 5-year disease survival rate of 30.5%. For resectable adenocarcinoma, the National Cancer Institute reports an overall five-year survival rate of only 20%, whereas resectable leiomyosarcoma's survival rate is reported at approximately 50%. One study found the overall rate of metastatic spread of leiomyosarcoma ranged from 24–50%; this cancer most often spread to the liver. Five-year survival in 705 patients with leiomyosarcoma was reported at 28%. Surgery is the preferred treatment for smooth muscle tumors. Little benefit was found for irradiation or chemotherapy, or for these therapies combined. Patients over 75 years of age have a significantly poorer survival rate than younger people. In addition, patients with poorly differentiated tumors have a poorer prognosis than those with moderately or well-differentiated tumors. Survival rate decreases with progression of disease by stage: localized 47.6%; regional 31%; distant 5.2%.

Alternative and complementary therapies

Bovine and shark cartilage is currently being explored in **clinical trials** for antitumor properties, but as of mid-2001 there is not enough evidence to warrant its use. Some popular herbs that are purported to have therapeutic effects in cancer treatment include echinacea, garlic, ginseng, and ginger. Laboratory studies have shown that echinacea has the potential to control the growth of cancerous cells, but more studies are needed to confirm efficacy in humans. In addition, dosage and toxicity levels still need to be established. Some studies suggest that diets high in garlic reduce the risk of stomach, esophageal, and colon cancers. There is still debate regarding the best form of garlic to take—whole raw garlic or garlic in tablet form; aged or fresh garlic; garlic with odor or ''deodorized'' garlic. Ginger is often recommended for its beneficial effects on the digestive system, but evidence has not confirmed efficacy in cancer treatment. Ginseng in excessive amounts can be very toxic, causing vomiting, bleeding, and death. Patients should not take herbal remedies without consulting their physicians, particularly if they intend to combine the herbs with prescription drugs. Herb and drug combinations can sometimes result in toxic interactions.

Coping with cancer treatment

Pain is a common problem for people with some types of cancer, especially when the cancer grows and presses against other organs and nerves. Pain may also

be a side effect of treatment. However, pain can generally be relieved or reduced with prescription medicines or over-the-counter drugs as recommended by the doctor. Other ways to reduce pain, such as relaxation exercises, may also be useful. It is important for patients to report pain to their doctors, so that steps can be taken to help relieve it.

Depression may affect approximately 15–25% of cancer patients, particularly if the prognosis for recovery is poor. A number of antidepressant medications are available from physicians to alleviate feelings of depression. Counseling with a psychologist or psychiatrist also may help patients deal with depression.

Clinical trials

As of 2001, Glivec (STI-571, or imatinib mesylate) is in clinical trials for treatment of gastrointestinal stromal tumors, as well as for leukemia and glioblastoma, a type of brain tumor. An open trial (GIST trial SWOG-S0033) led by Southwest Oncology Group will test those individuals with metastatic or recurrent disease using two doses of the drug.

Clinical trials may be suitable for patients suffering from small intestine cancer. The principal investigator should be contacted regarding participation in appropriate trials. For information about cancer trials, patients can visit the National Cancer Institute web site at <http://cancertrials.nci.nih.gov>.

Prevention

Most people who develop cancer do not have inherited genetic abnormalities. Their genes have been damaged after birth by substances in their environment. A substance that damages deoxyribonucleic acid (DNA) in a way that can lead to cancer is called a carcinogen. Carcinogens include certain chemicals, certain types of radiation, and viruses. Asbestos is one substance that is suspected of contributing to the development of small intestinal cancer. Although the precise causes of cancer are not known, a variety of factors are known to contribute to the development of cancer including tobacco smoke, and poor dietary habits such as high-fat diet. Eating a diet rich in fruits and vegetables and low in fat may reduce the likelihood of cancer. Studies have demonstrated that individuals who were protected from cancer ate a greater variety of foods and nutrients compared to those with cancer. Several fruits, vitamins, and minerals were found particularly protective against intestinal cancer including vitamin B_6, folate, niacin, and iron. Some studies have linked eating large amounts of salt-cured, salt-pickled, and smoked foods to cancers of the digestive system. Other studies have linked stomach cancers, specifically intestinal cancer, to a lack of fruits, vegetables, and fiber in the diet. For prevention of cancer, it is important to avoid carcinogens (smoking, chemicals) and known risk factors, and to pursue a healthy lifestyle which includes moderate alcohol intake, regular exercise, a low-fat diet, and a diet rich in fruits and vegetables. Modifying genetic predispositions through risk factor reduction can also assist in prevention.

KEY TERMS

Adenocarcinoma—A cancer that starts in glandular tissue.

Angiosarcoma—A malignant tumor that develops either from blood vessels or from lymphatic vessels.

Carcinogen—A substance that causes cancer.

Carcinoid—A tumor that develops from neuroendocrine cells.

Leiomyosarcoma—A cancerous tumor of smooth (involuntary) muscle tissue.

Liposarcoma—A cancerous tumor of fat tissue.

Lymphoma—A cancer of the lymphatic tissue.

Malignant—Cancerous; a tumor or growth that often destroys surrounding tissue and spreads to other parts of the body.

Metastasis—The spread of cancer from the original site to other body parts.

Radiation therapy—Also called radiotherapy, it uses high-energy rays to kill cancer cells.

Sarcoma—A malignant tumor of the soft tissue including fat, muscle, nerve, joint, blood vessel, and deep skin tissues.

Staging—Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body.

Special concerns

Due to the side effects of radiation and chemotherapy, individuals must make a deliberate effort to eat as nutritiously as possible. Those who experience pain, nausea, or diarrhea may want to discuss treatments options with their doctor to ease these side effects.

Eating well during cancer treatment means getting enough calories and protein to help prevent weight loss

QUESTIONS TO ASK THE DOCTOR

- What is my diagnosis?
- Is there any evidence the cancer has spread?
- What is the stage of the disease?
- What are my treatment choices?
- What new treatments are being studied?
- Would a clinical trial be appropriate for me?
- What are the expected benefits of each kind of treatment?
- What are the risks and possible side effects of each treatment?
- How often will I have treatments?
- How long will treatment last?
- Will I have to change my normal activities?
- What is the treatment likely to cost?
- Is infertility a side effect of cancer treatment? Can anything be done about it?
- What is my prognosis?

and maintain strength. Eating nutritiously may also help an individual feel better.

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The National Cancer Institute (NCI). For information contact the Public Inquiries Office: Building 31, Room 10A31, 31 Center Drive, MSC 2580, Betheseda, MD 20892-2580 USA. (301) 435-3848 or 1-800-4-CANCER. <http://cancer.gov/publications/> or <http://cancertrials.nci.nih.gov> or <http://cancernet.nci.nih.gov>.

National Center for Complementary and Alternative Medicine (NCCAM). 31 Center Dr., Room #5B-58, Bethesda, MD 20892-2182. (800) NIH-NCAM. Fax: (301) 495-4957. <http://nccam.nih.gov>.

Crystal Heather Kaczkowski, MSc.

Smoking cessation

Definition

Smoking cessation is the medical term for quitting smoking. It is a vital part of **cancer prevention** because smoking is the single most preventable cause of death from cancer. As early as 1982, the Surgeon General reported that tobacco causes more cancer deaths in the United States than any other factor–30% of all cancer deaths, including 87% of deaths from lung cancer. Although people think of smoking most often in connection with lung cancer, smoking is also associated with cancers of the mouth, throat, voice box (larynx), esophagus, pancreas, kidney, and bladder. Women who smoke increase their risk of cancer of the cervix. Quitting smoking, however, significantly reduces the risk of cancer; 15 years after quitting, a former smoker's risk is almost as low as that of someone who has never smoked.

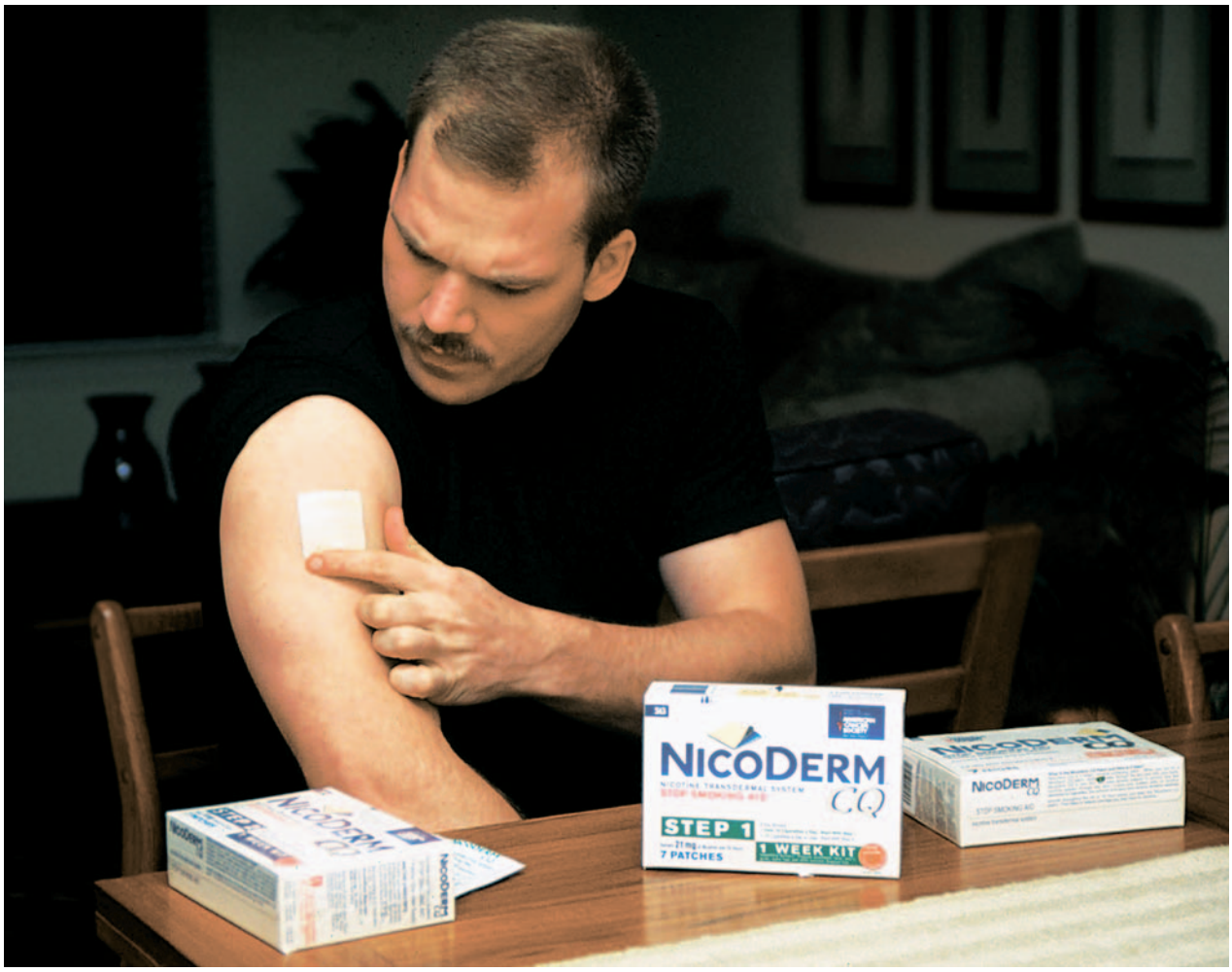
Description

Smoking cessation covers several different approaches, ranging from medications and psychotherapy to special classes and programs. Smoking is a habit difficult to break because it involves many different aspects of a person's emotions and social life as well as physical addiction to nicotine. Most people who quit smoking successfully use a combination of treatments or techniques for quitting.

Special concerns

People who are trying to quit smoking are often concerned about:

- Withdrawal symptoms. Nicotine, the substance in tobacco that gives smokers a pleasurable feeling, is as addictive as heroin or cocaine. Withdrawal from nicotine may produce **depression**, anger, fatigue, headaches, problems with sleep or concentration, or increased appetite for food. These symptoms usually start several hours after the last cigarette. They may last for several days or several weeks.
- Weight gain. Many people, particularly women, gain between two and 10 pounds after giving up smoking.



A man with a nicotine patch. *(Photo Researchers, Inc. Reproduced by permission.)*

This mild weight gain, however, is not nearly as great a danger to health as continuing to smoke. Getting more exercise can help.

- Stress. Many smokers started to smoke as a way to cope with stress and tension. Finding other methods—exercise, meditation, biofeedback, massage, and others, can reduce the temptation to smoke when stress arises.
- Side effects of nicotine replacement products. Smokers who are using these products to help them quit may experience headaches, nausea, sore throat, or long-term dependence. Side effects can often be reduced or eliminated by using a lower dosage of the product or switching to another form of nicotine replacement.

Treatments

Nicotine replacement therapy

Nicotine replacement therapy gives the smoker a measured supply of nicotine without the other harmful chemicals in tobacco. It reduces the physical craving for **cigarettes** so that the smoker can handle the psychological aspects of quitting more effectively.

As of 2001, the Food and Drug Administration (FDA) had approved four forms of nicotine replacement therapy:

- Transdermal patches. Patches, which are non-prescription items, supply measured doses of nicotine through the skin. The doses are lowered over a period of weeks, thus helping the smoker to reduce the need for nicotine gradually.
- Nicotine gum. Nicotine gum provides a fast-acting nicotine replacement that is absorbed through the mouth tissues. The smoker chews the gum slowly and then keeps it against the inside of the cheek for 20 to 30 minutes. The gum is also available without prescription.
- Nasal spray. Nicotine nasal spray provides nicotine through the tissues that line the nose. It acts much more

KEY TERMS

Bupropion—An antidepressant medication given to smokers for nicotine withdrawal symptoms. It is sold under the trade name Zyban.

Buspirone—An anti-anxiety medication that is also given for withdrawal symptoms. It is sold under the trade name BuSpar.

Nicotine—A colorless, oily chemical found in tobacco that makes people physically dependent on smoking. It is poisonous in large doses.

QUESTIONS TO ASK THE DOCTOR

- What methods would you recommend to help me quit smoking?
- How can I cope with withdrawal symptoms and other side effects of quitting?
- Are there any stop-smoking programs in this area that you would recommend?

rapidly than the patches or gum, but requires a doctor's prescription.

- Inhalers. Nicotine inhalers are plastic tubes containing nicotine plugs. The plug gives off nicotine vapor when the smoker puffs on the tube. Some smokers prefer inhalers because they look more like cigarettes than other types of nicotine replacement. They also require a doctor's prescription.

Other medications

Bupropion, which is sold under the trade name Zyban, is an antidepressant medication given to lower the symptoms of withdrawal from nicotine. Bupropion by itself can help people quit smoking, but its success rate is even higher when it is used together with nicotine replacement therapy. Another drug that is sometimes given for nicotine withdrawal is buspirone (BuSpar), which is an antianxiety medication.

Stop-smoking programs and groups

Stop-smoking programs help by reinforcing a smoker's decision to give up tobacco. They teach people to recognize common problems that occur during quitting and they offer emotional support and encouragement. While stop-smoking programs do not have as high a success rate by themselves as medications or nicotine replacement therapy, they are very helpful as part of an overall quitting plan. The most effective programs include either individual or group psychological counseling. Many state Medicaid plans now cover the costs of smoking cessation programs; further information is available from the American Association of Respiratory Care at <http://www.aarc.org/advocacy/state/smoking_treatment.html.>

The Great American Smokeout has been held annually since 1977 on the third Thursday in November to call attention to the high human costs of smoking. Smokers are asked to quit for the day and donate the money saved on cigarettes to high school scholarship funds.

Nicotine Anonymous is an organization that applies the Twelve Steps of Alcoholics Anonymous (AA) to tobacco addiction. Its group meetings are free of charge.

Alternative and complementary therapies

Some people find that hypnosis helps them to quit. Acupuncture has also been used, but there are no large-scale studies comparing it to other stop-smoking treatments. A list of physicians who are also licensed acupuncturists is available from the American Academy of Medical Acupuncture at (800) 521-2262.

Other complementary approaches that have been shown to be useful in quitting smoking include movement therapies like yoga, t'ai chi, and dance. Prayer and meditation have also helped many smokers learn to handle stress without using tobacco.

See also Cigarettes.

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Rebecca J. Frey, Ph.D.

Sodium iodide I 131 *see* **Radiopharmaceuticals**

Sodium phosphate P 32 *see* **Radiopharmaceuticals**

Soft tissue sarcoma

Definition

Soft tissue sarcomas are cancerous (malignant) tumors that develop in mesodermal tissues that surround, support, and connect the structures and organs of the body.

Description

Soft tissues include muscles, fibrous (connective) tissues, fat, blood and lymph vessels, synovial tissues surrounding the joints, peripheral nerve tissues, and deep skin tissues. As soft tissue sarcomas grow, they may invade surrounding tissue, or spread (metastasize) to distant sites in the body. Together they account for less than 1% of all newly diagnosed cancers.

About one-half of all soft tissue sarcomas develop in the arms, legs, hands, or feet. About 40% occur in the trunk, internal organs, or the retroperitoneum—the back of the abdominal cavity. The remaining 10% occur in the head and neck.

Muscle tissue sarcomas

Rhabdomyosarcoma (RMS)—a skeletal muscle tumor—is the most common soft tissue **sarcoma** in children. Embryonal rhabdomyosarcoma (ERMS) is more common than alveolar rhabdomyosarcoma (ARMS). ERMS commonly develops in the head, neck, or reproductive or urinary tract organs. ARMS develops in the large muscles of the arms, legs, or trunk. All other soft tissue sarcomas in children are classified as non-rhabdomyosarcoma or non-RMS.

Leiomyosarcomas are smooth muscle tumors that occur most often in the retroperitoneum or internal organs but also may occur in the deep soft tissues of the arms or legs.

Fibrous tissue sarcomas

Soft tissue sarcomas often occur in connective tissue:

- **Fibrosarcoma** is a cancer of the tendons and ligaments.
- Malignant fibrous histiocytoma (MFH) is the most common soft tissue tumor of the limbs, although it also occurs in the retroperitoneum. MFH accounts for 40% of all soft tissue sarcomas.
- Dermatofibrosarcoma protuberans (DFSP) is a low-grade cancer of fibrous tissue under the skin, usually in the limbs or trunk.
- Desmoid tumors may be low-grade fibrosarcomas or a unique type of fibrous tissue tumor.

Fat tissue sarcomas

Liposarcomas develop in fat tissue anywhere in the body but occur most often in the thigh or the retroperitoneum. They range from very slow to very fast growing and account for 25% of all soft tissue sarcomas.

Blood and lymph vessel sarcomas

- Angiosarcoma is called hemangiosarcoma if it occurs in a blood vessel and lymphangiosarcoma if it occurs in a lymph vessel.
- Hemangioendothelioma—usually called epithelioid hemangioendothelioma (EHE) in adults—is a low-grade cancer in the blood vessels of soft tissue or internal organs such as the lungs or liver.
- Hemangiopericytoma is a sarcoma of the perivascular tissue around blood vessels that help control blood

flow. It most often develops in the legs, pelvis, or retroperitoneum.

- Kaposi's sarcoma is a tumor formed by cells similar to those that line blood and lymph vessels.

Synovial sarcoma

Synovial sarcomas are tumors of the synovium—the tough tissue that surrounds the joints. They occur most often in leg and arm joints, especially the knee. They are the most common non-RMS in children. Approximately 30% of synovial sarcomas occur in those under age 20.

Peripheral nerve sarcomas

Malignant peripheral nerve sheath tumors—also called malignant schwannomas, neurofibrosarcomas, or neurogenic sarcomas—are tumors in cells surrounding the peripheral nerves that run throughout the body. Ewing's tumors are a group of related cancers that share characteristics with nerve tissue in a developing embryo. Ewing's tumors that occur in soft tissue are extraosseous (outside of the bone) Ewing's (EOE) and primitive neuroectodermal tumors (PNET).

Other soft tissue sarcomas

Some soft tissue sarcomas are of uncertain origin:

- Mesenchymonia is a combination of tissue types that resemble fibrosarcoma and others.
- Alveolar soft-part sarcoma most commonly develops in the legs.
- Epithelioid sarcoma usually develops under the skin of the hands, forearms, lower legs, or feet.
- Clear cell sarcoma—also called malignant **melanoma** of the soft parts (MMSP), clear cell sarcoma of tendons, aponeuroses—is a rare sarcoma of the tendons and related tissues. It has some characteristics of malignant melanoma or skin cancer.
- Desmoplastic small cell tumors usually occur in the abdomen, pelvis, or tissues around the testes, primarily in males.

Demographics

It is estimated that 9,420 new cases of soft tissue sarcomas will be diagnosed in the United States during 2005—5,530 in males and 3,890 in females. Every year in the United States 850–900 children under age 20 are diagnosed with soft tissue sarcoma, accounting for 7.4% of cancers in that age group. During 2005 an estimated 1,910 American males and 1,580 females will die of soft tissue sarcoma.

Childhood soft tissue sarcomas occur most frequently during infancy or after age 10. Male children have a slightly higher incidence than females and black children have a slightly higher incidence than white children, particularly among 15–19-year-olds.

More than 85% of RMS occur in infants, children, and teenagers. Almost 60% of soft tissue sarcomas in children up to age four are RMS. The prevalence of RMS declines steadily with increasing age, accounting for only 23% of soft tissue sarcomas in 16–19-year-olds. ERMS accounts for 75% of RMS in children aged 1–14. ARMS can affect children in all age groups but is more prevalent among older children.

Other soft tissue sarcomas also affect different age groups:

- Adolescents are more likely to develop **leiomyosarcoma** in the trunk, whereas in adults it is more common in the uterus or digestive tract.
- Infantile fibrosarcoma affects children up to age four.
- Adolescents are more likely to develop fibrosarcoma in the arms or legs and MFH in the legs.
- Adults are more likely to develop fibrosarcoma in the arms, legs, or trunk, or DFSP in the trunk; MFH is most common in older adults.
- Liposcarcoma can occur in the arms and legs of older teenagers and in the arms, legs, or trunk of adults; however it is most common in people aged 60–65.
- Adults are more likely to develop hemangiosarcoma in the arms, legs, or trunk, lymphangiosarcoma in the arms, or Kaposi's sarcoma in the legs or trunk.
- Hemangiopericytoma is more common in adults, although infantile hemangiopericytoma occurs in children up to age four.
- Synovial sarcomas usually occur in young adults.
- Teenagers and adults can develop malignant peripheral nerve sheath tumors in the arms, legs, or trunk.
- Soft tissue Ewing's tumors are relatively common in children and very rare in adults.
- Mesenchymonia is a rare sarcoma of children.
- Aveolar soft-part sarcoma is rare, usually affecting young adults.
- Alveolar soft-part sarcoma of the muscular nerves of the arms or legs can affect children in all age groups but is more prevalent in older children.
- Epithelioid sarcoma usually affects adolescents and young adults.
- Desmoplastic small cell tumors are rare and affect primarily male teenagers and young adults.

Causes & symptoms

Causes

Although most soft tissue sarcomas have no known cause, those in children generally are associated with chromosomal changes. Other soft tissue sarcomas are caused by changes in the DNA carried on the chromosomes. Some of these changes or mutations are inherited but most are acquired during a person's lifetime, possibly from exposure to radiation or cancer-causing chemicals.

In addition:

- Leiomyosarcoma and some other soft tissue sarcomas have been linked to the **Epstein-Barr virus** in people with AIDS.
- Some hormones, particularly estrogen, cause desmoid tumors to grow.
- Angiosarcomas sometimes develop in an area that has been exposed to radiation.
- Kaposi's sarcoma appears to be related to infection by human herpesvirus-8.

Symptoms

During their early stages most soft tissue sarcomas do not cause symptoms. However as they grow larger the tumors begin to press against normal tissue causing soreness or pain. Synovial sarcoma causes tenderness, pain, or swelling in a joint.

Symptoms of soft tissue sarcoma can include:

- a new or growing lump anywhere in the body
- a usually painless swelling or lump in an arm or leg that grows over weeks or months.

About one-third of abdominal sarcomas cause increasing pain. Although symptoms may be nonspecific, abdominal tumors can grow large enough to be felt or to cause blockage or bleeding in the stomach or bowels. This leads to blood in vomit or stools and may cause stools to be very black and tarry.

RMS often develops in easily detectable regions such as a lump just under the skin or around the testes:

- RMS in an eye muscle can cause bulging eye
- RMS in the nasal cavity may cause nosebleeds
- RMS often occurs in the bladder or genitourinary tract causing difficult urination or blood in the urine
- RMS in the abdomen or pelvis may cause vomiting, abdominal pain, or constipation

Diagnosis

Only about 50% of soft tissue sarcomas are diagnosed at early stages before the cancer has spread. Soft tissue sarcomas in children may be particularly difficult to diagnose.

Diagnosis may include:

- a medical history to uncover any risk factors
- a physical examination
- ultrasound imaging for visualizing internal organs and masses
- a **computed tomography** (CT) scan—sometimes in conjunction with a radiocontrast dye—to help determine whether a sarcoma has spread to the liver or other organs
- magnetic resonance imaging (MRI)—sometimes with radiocontrast dyes—to obtain detailed images of organs or masses
- chest **x rays** to determine whether a sarcoma has spread to the lungs
- positron emission tomography (PET) to scan the entire body for metastasized cancer

Biopsies

Unlike most cancers, the size of a soft tissue sarcoma may be less important than the appearance of the cancer cell. Cells that appear similar to normal cells of the same tissue are called well-differentiated or moderately differentiated. Sarcoma cells that appear very different from normal tissue are referred to as poorly differentiated or undifferentiated. For example, ERMS cells resemble developing skeletal muscle cells in a 6–8-week-old fetus and ARMS cells resemble the normal muscle cells of a 10-week-old fetus. Therefore microscopic examination of sarcoma cells obtained by a biopsy—the removal of sarcoma tissue—is very important for determining the clinical stage, the probable growth rate of the cancer, the likelihood of **metastasis**, and the prognosis.

A fine needle aspiration (FNA) **biopsy** uses a very thin needle and syringe to remove small fragments of a superficial (near the surface), easily accessed sarcoma. The needle may be guided by feeling a mass near the surface or using a CT scanner. Although much less invasive than other types of biopsies, FNA may not provide enough tissue to identify a sarcoma, determine its type, and grade it. However it is useful for determining whether a suspected sarcoma is a benign tumor, another type of cancer, an infection, or some other disease. FNA also is used to determine whether tumors in other organs are metastases of the sarcoma.

If FNA indicates a sarcoma, another type of biopsy is used to confirm the diagnosis:

- A core needle biopsy removes a cylindrical piece of tissue of about one-sixteenth in. (0.15 cm) diameter

and 0.5 in. (1.3 cm) long. A CT scanner may be used to guide the needle into tumors located in internal organs. Although a core biopsy avoids an incision and may not require general anesthesia, the small sample size may cause a cancer to be missed or misdiagnosed.

- If the sarcoma is small, near the surface, and away from vital tissues, an excisional biopsy may be used to remove the entire mass and surrounding normal tissue. This combines a diagnostic biopsy with surgical treatment.
- An incisional biopsy removes a small portion of a large sarcoma.
- An open surgical biopsy under general anesthesia is used to diagnose RMS in children. In addition to the tumor sample, nearby lymph nodes may be removed for testing.

Testing

In addition to histological examination under a microscope, biopsy samples may require special testing to identify a sarcoma and its type and grade:

- An immunohistochemical test treats the sample with antibodies that recognize cell proteins that are typical of some types of sarcomas. When an antibody binds such a cell protein, a color change is detected microscopically.
- For cytogenetic techniques biopsied cells are grown in the laboratory for about a week and examined microscopically to determine whether chromosomal changes have occurred.
- Fluorescent *in situ* hybridization (FISH) may be used to detect chromosome abnormalities without first growing the cells.

Treatment team

Soft tissue sarcomas are treated by a multidisciplinary team of cancer specialists including:

- pathologists
- hematologists
- oncologists
- surgeons
- radiation oncologists

Children and adolescents with soft tissue sarcomas are treated at medical centers specializing in **childhood cancers** with treatment teams that include:

- a primary care physician
- pediatric hematologists/oncologists
- pediatric surgeons
- radiation oncologists
- pediatric oncology nurses
- nurse practitioners
- rehabilitation and physical therapists
- psychologists
- child-life specialists
- nutritionists
- social workers
- educators

Clinical staging, treatments, and prognosis

Staging systems

TNM Soft tissue sarcomas often are staged according to the TNM system of the American Joint Committee on Cancer, in which T is the primary tumor size and location:

- TX—cannot be assessed
- T0—no evidence of a primary tumor
- T1—the sarcoma is 2 in. (5 cm) or less
- T2—the sarcoma is more than 2 in. (5 cm)
- a—the tumor is superficial
- b—the tumor is deep in a limb or the abdomen.

N represents lymph node involvement in the region of the sarcoma:

- NX—cannot be assessed
- NO—lymph nodes free of sarcoma cells
- N1—regional lymph nodes have sarcoma cells.

Although RMS and synovial and epithelioid sarcomas commonly spread to lymph nodes, overall lymph node involvement occurs with less than 3% of adult soft tissue sarcomas.

M represents metastasis to distant organs:

- MX—cannot be assessed
- MO—sarcoma has not spread
- M1—distant metastases

GRADING In addition to a standard staging system, soft tissue sarcomas are graded according to the microscopic appearance of the cells, where G is the histological grade:

- GX—cannot be assessed
- G1 or low grade—cells appear normal, well-differentiated, slow-growing; these rarely metastasize

- G2 or intermediate—cells are moderately differentiated and fast growing
- G3 or high grade—cells are poorly differentiated and faster growing
- G4—cells are abnormal, poorly or undifferentiated, and very fast growing.

Clinical staging

Stage I sarcomas are low-grade cancers:

- Stage IA—G1–2, T1a or b, N0, M0
- Stage IB—G1–2, T2a, N0, M0

Stage II, III, and IV sarcomas are high-grade cancers:

- Stage IIA—G1–2, T2b, N0, M0
- Stage IIB—G3–4, T1a–b, N0, M0
- Stage IIC—G3—4, T2a, N0, M0
- Stage III—G3–4, T2b, N0, M0
- Stage IVA—any G, any T, N1, M0
- Stage IVB—any G, any T, any N, M1.

Treatments

In addition to the stage, treatment depends on other factors including the location of the sarcoma. Treatment of children with non-RMS usually follows the standard treatment for adults. However potential long-term effects of treatment are a greater concern in children, who are much more susceptible to radiation and are expected to live much longer than adults.

SURGERY Most stage I, II, and III soft tissue sarcomas are surgically removed, with the goal of completely removing (resectioning) the tumor, as well as at least 0.8–1.2 in. (2–3 cm) of surrounding tissue. Many soft tissue sarcomas in infants and young children can be treated successfully by surgery alone. Only about 5% of arm or leg sarcomas require **amputation** of the limb. Most patients have limb-sparing surgery followed by **radiation therapy**, although these procedures are more difficult in children than in adults. Amputation may be necessary when invading sarcoma cells surround essential nerves, arteries, or muscles, or when limb-sparing surgery would result in a dysfunctional limb or chronic pain. Amputation is not recommended if the sarcoma has metastasized to the lungs or other organs. Abdominal sarcomas are difficult to remove because they can be quite large and adjacent to vital organs.

Stage IVA sarcomas and nearby lymph nodes are surgically removed. Sometimes the removal of stage IVB sarcomas and all of their metastases is attempted. Surgery may be preceded by high-dose radiation and/or **chemotherapy** to shrink the tumor or for high-grade sarcomas that are at risk of metastasizing. If the only metastasis is in the lungs, sometimes the lung tumor can be removed.

RADIATION THERAPY Radiation therapy uses high-energy rays such as x rays to kill cancer cells:

- External beam radiation—delivered from outside the body—is aimed directly into the sarcoma and is the most common radiation treatment for soft tissue sarcomas.
- Internal radiation therapy (brachytherapy) delivers small pellets of radioactive material directly into the sarcoma through thin plastic tubes. It may be used alone or in combination with external beam radiation.

Radiation may be used:

- before and/or after surgery for all sarcoma stages
- for inoperable stage I and II sarcomas
- as the primary treatment for patients with health conditions that preclude surgery
- to kill small clusters of cancer cells
- to relieve symptoms of stage IVB sarcoma
- as an adjunct treatment 6–9 weeks after chemotherapy
- for recurrent sarcomas that were not treated previously with radiation
- to treat pain accompanying recurrences

Tumors of the retroperitoneum, trunk, head, or neck may be treated with fast neutron therapy.

Short-term side effects of radiation therapy may include:

- fatigue
- mild skin conditions
- infections
- nausea, vomiting, and **diarrhea** after irradiation of the abdomen
- mouth sores and loss of appetite after head or neck irradiation
- swelling, weakness, or pain following irradiation of large portions of a limb

Longer-term radiation effects can include:

- worsening of chemotherapy side effects
- breathing difficulties and lung damage from chest irradiation
- bone fractures, sometimes occurring years later
- headaches and mental problems one to two years after radiation therapy for metastatic sarcoma in the brain

CHEMOTHERAPY Chemotherapy may be used:

- as primary therapy for some sarcomas
- to shrink a stage II tumor prior to surgery
- as postoperative treatment for stage II sarcomas
- before or after surgery for stage III sarcomas to reduce the risk of recurrence
- to treat metastasized sarcomas
- to reduce pain with stage IV sarcomas
- for recurrence at a distant site

Synovial sarcomas respond more readily to chemotherapy than other soft tissue sarcomas. Chemotherapy usually does not prevent metastasis and the benefits of postoperative chemotherapy in children have been questioned.

Ifosfamide and **doxorubicin** (Adriamycin) are the most common drugs for treating soft tissue sarcoma. They may be used alone, together, or in combination with other drugs including:

- **dacarbazine**
- methotrexate
- **vincristine**
- cisplatin
- paclitaxel
- mesna for protecting the bladder from severe irritation caused by ifosfamide

When used alone only doxorubicin and ifosfamide have response rates above 20%. Doxorubicin alone or in combination with dacarbazine is the most frequently used chemotherapy for advanced sarcomas. High-dose ifosfamide is used to relieve symptoms of inoperable sarcomas.

Postoperative chemotherapy for ERMS is usually vincristine and **dactinomycin** (actinomycin-D). For group II and III RMS, **cyclophosphamide** is added for a three-drug combination called VAC. **Topotecan** also may be included.

Temporary side effects of chemotherapy may include:

- nausea and vomiting
- loss of appetite
- hair loss
- mouth sores

Chemotherpy can damage blood-producing bone marrow cells, increasing the risk of:

- fatigue
- bruising or bleeding
- infection

Most side effects disappear when chemotherapy ends, although it sometimes causes infertility. Doxorubicin can weaken the heart and ifosfamide and cyclophosphamide can cause permanent kidney or bladder damage.

RECURRENCES Treatment of recurrent soft tissue sarcomas depends on the initial type and treatment. If the initial treatment was minimal, a local recurrence may be treated with surgery and radiation. If the original treatment was aggressive, limb amputation may be necessary. The lungs are the most common distant site of sarcoma recurrences, usually within two to three years after the initial diagnosis. These are treated as stage IV disease. In older patients symptoms of recurrence may be treated by the sequential use of single chemotherapy drugs. Synovial sarcomas tend to recur locally and involve regional lymph nodes; however distant metastasis occurs in about 50% of cases, sometimes many years later.

Prognosis

Stage I and II soft tissue sarcomas rarely metastasize although they may recur locally if inadequately treated:

- Stage I sarcomas have a five-year-survival rate of 99% and only a 20% chance of recurrence within five years.
- Stage II sarcomas have an 82%-five-year-survival rate and a five-year-recurrence risk of 35%.
- Stage III sarcomas have a five-year-survival rate of 50% and a five-year-recurrence risk of about 65%.
- Stage IV sarcomas are usually incurable with a five-year-survival rate of 10–15%.
- Surgery to remove metastatic lung sarcomas has a five-year-survival rate of 20–30% and occasionally a complete cure.
- Patients over age 60 have a poorer prognosis than younger adults.

In children:

- stage I: 90% never have a recurrence
- stage II: about 89% survive long term and about 50% of recurrences are cured in the second round of treatment
- stage III: about 70% survive long term
- stage IV: a five-year-survival rate of less than 30%, although children under age 10 with metastatic embryonal tumors have a 50% chance of survival.

Younger children with RMS have higher survival rates than older children and adolescents and ERMS has a more favorable prognosis than ARMS. More than 70% of children survive ERMS and second malignancies arise in less than 25% of survivors, usually in children with more advanced disease.

KEY TERMS

Alveolar rhabdomyosarcoma, ARMS—A type of soft tissue sarcoma in the large muscles of the arms, legs, or trunk that primarily affects older children.

Brachytherapy—Irradiation in direct contact with a sarcoma.

Cytogenetics—The combined study of heredity and the structure and function of cells.

Dermatofibrosarcoma protuberans, DFSP—A low-grade cancer of fibrous tissue under the skin, usually in the limbs or trunk.

Embryonal rhabdomyosarcoma, ERMS—The most common type of RMS in children, occurring in the head, neck, or genitourinary tract and resembling fetal skeletal muscle tissue.

Epithelioid hemangioendothelioma, EHE—Hemangioendothelioma in adults.

Extraosseous Ewing's tumor, EOE—A type of Ewing's tumor in soft tissue outside of the bone tissue with some characteristics of embryonic nerve tissue.

Hemangioendothelioma—A low-grade sarcoma of the blood vessels of soft tissues or internal organs such as the lungs or liver.

Fine needle aspiration, FNA—A type of biopsy that uses a very thin needle to remove small pieces of a superficial suspected sarcoma.

Lymph nodes—The filtering system for the lymph that carries white blood cells of the immune system throughout the body via lymph vessels.

Mesoderm—The middle layer of embryonic cells that gives rise to skin, connective tissue, blood and lymph vessels, the urogenital system, and most muscles.

Malignant fibrous histiocytoma, MFH—The most common soft tissue tumor of the limbs, occurring primarily in older adults and accounting for 40% of all soft tissue sarcomas.

Primitive neuroectodermal tumor, PNET—A type of Ewing's tumor in soft tissue with some characteristics of embryonic nerve tissue.

Non-RMS—All soft tissue sarcomas in children that are not RMS.

Retroperitoneum—The space between the lining of the abdominal and pelvic walls and the back wall of the body.

Rhabdomyosarcoma, RMS—A cancerous tumor of the skeletal muscle and the most common soft tissue sarcoma in children.

TNM—A cancer staging system in which T is the primary tumor size and location, N is lymph node involvement, and M is metastasis to distant parts of the body.

Children with non-RMS generally have a better prognosis than adults, although if the sarcoma is not removed completely, metastasizes, or recurs, the prognosis is poor:

- Leiomyosarcoma has a good prognosis unless it is within the gastrointestinal tract.
- Infantile fibrosarcoma—which occurs in children under five—has an excellent prognosis when treated with surgery alone.
- Adult-type fibrosarcomas have a survival rate of about 60% in both children and adults.
- MFH has a survival rate of about 50%.
- Desmoid tumors rarely metastasize and have an excellent prognosis.
- Liposarcomas have a good prognosis if completely removed.
- The prognosis for angiosarcomas and hemangioendotheliomas depends on their removal, the extent of the disease, and the grade of the malignancy.
- Hemangiopericytoma has an excellent prognosis in young children and an overall survival rate of 30–70%.
- Synovial sarcoma has a survival rate of 80%.
- Neurofibrosarcoma has a very good prognosis with complete removal; otherwise the prognosis is poor.
- Alveolar and clear cell soft-part sarcomas have a 50% survival rate and late relapses are common.

High-grade retroperitoneal sarcoma has a less favorable prognosis because of the difficulty of completely removing the tumor and the limitations on high-dose radiation therapy. Local recurrence is the most common cause of death in these patients.

Clinical trials

As of 2005 numerous **clinical trials** for treating soft tissue sarcomas in children and adults were underway, including trials to evaluate:

- chemotherapy prior to surgery

- regional chemotherapy in which drugs are injected directly into the artery that supplies an affected limb
- new drugs for reducing heart damage from doxorubicin, so that higher doses can be used
- the use of radiation therapy during surgery for abdominal and retroperitoneal sarcomas
- drugs such as interleukin-2 to boost the immune system
- vaccines that may cause the immune system to recognize abnormal chemicals in sarcomas and destroy the cells
- stem-cell transplantations that allow higher levels of chemotherapy for treating RMS.

Prevention

Most soft tissue sarcomas develop in people with no known risk factors. Since early detection is very important, a healthcare professional should be consulted about unexplained lumps, growths, or other symptoms. Less than 5% of soft tissue sarcomas are caused by radiation exposure. Lymphangiosarcomas can develop where lymph nodes have been damaged by radiation or surgically removed.

A high percentage of patients with angiosarcoma of the liver have been exposed to vinyl chloride. Although exposures to other chemicals—including dioxin, herbicides containing phenoxyacetic acid, and chlorophenols in wood preservations—have been suggested as risk factors for soft tissue sarcoma, there are no proven connections.

The only known risk factors in children are congenital (present at birth) abnormalities and genetic (inherited) conditions:

- Li-Fraumeni syndrome increases the risk of soft tissue sarcomas as well as other types of cancer and there is a high risk of developing soft tissue sarcoma in an area that was irradiated to treat another cancer.
- Children with inherited retinoblastoma—an eye cancer—are at increased risk for soft tissue sarcoma.
- Children with Beckwith-Wiedemann syndrome are at risk for developing RMS.
- Gardner's syndrome increases the risk of desmoid tumors in the abdomen.
- Neurofibromatosis or von Recklinghausen's disease is characterized by benign neurofibromas; in about 5% of cases these develop into malignant peripheral nerve sheath tumors.

Those with a family history of sarcomas or other cancers occurring at a young age may have **genetic testing** to assess their risk.

QUESTIONS TO ASK YOUR DOCTOR

- What type of sarcoma do I have?
- Has the cancer spread?
- What stage is the cancer and what does that mean for me?
- What are the treatment options?
- What treatment do you recommend and why?
- What are the risks and side effects of each treatment?
- What are the risks of recurrence after each treatment?
- How should I prepare for the treatment?
- How much work or school will be missed?
- What is the recovery time after treatment?
- What is my estimated survival time?

Special concerns

Since advanced soft tissue sarcoma has a high risk of metastasis and recurrence, following treatment a patient may have:

- frequent physical examinations
- chest x rays, ultrasound, or CT or MRI scans

See also AIDS-related cancers; Osteosarcoma.

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ORGANIZATIONS

American Cancer Society. PO Box 102454, Atlanta, GA 30368-2454. 800-ACS-2345. <http://www.cancer.org>. Information, research, and patient support.

CureSearch. 4600 East West Highway, #600, Bethesda, MD 20814-3457. 800-458-6223. 240-235-2200. <http://www.curesearch.org>. Children's Oncology Group and the National Childhood Cancer Foundation. Information, research, and advocacy.

National Cancer Institute. Public Inquiries Office, Suite 30361, 6116 Executive Blvd., MSC-8322, Bethesda, MD 20892-8322. 800-4-CANCER (800-422-6237). <http://www.nci.nih.gov>. Information, research, and clinical trials.

National Children's Cancer Society. 1015 Locust, Suite 600, St. Louis, MO 63101. 800-5-FAMILY (800-532-6459). 314-241-1600. <http://nationalchildrenscancersociety.com<. Financial assistance, support services, advocacy, and education.

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Sperm banking *see* **Fertility issues**

Spinal axis tumors

Definition

Spinal axis tumors are tumors that affect the spinal cord—the bundle of nerves that lies inside the backbone. Another term for spinal axis tumors is spinal cord tumors.

Description

Spinal axis tumors form on or near the spinal cord and produce pressure on the associated nerves and blood vessels. There are three types of spinal axis tumors: extradural, extramedullary intradural, and intramedullary.

Extradural spinal axis tumors

Extradural tumors are found outside the dura mater, the membrane that encases the spinal cord. Extradural tumors are wedged between the dura mater and the bone of the spine. Types of extradural tumors include chordomas, osteoblastomas, osteomas, and hemangiomas.

Extramedullary intradural spinal axis tumors

Extramedullary intradural tumors are found inside the dura mater but outside the nerves of the spinal cord itself. Types of extramedullary tumors include meningiomas and neurofibromas.

Intramedullary spinal axis tumors

Intramedullary tumors are found inside the nerves of the spinal cord. Types of intramedullary tumors include astrocytomas, ependymomas, and hemangioblastomas.

Benign vs. malignant

Spinal axis tumors are classified as either benign or malignant. The cells of malignant tumors are very different from normal cells, grow quickly, and usually spread easily to other parts of the body. Benign tumors have cells that are similar to normal cells, grow slowly, and tend to be localized. However, even benign tumors can cause significant problems when they grow within the confined space inside the backbone.

Demographics

Primary spinal axis tumors, or tumors that originate in the spinal axis itself, are extremely rare and represent only 0.5% of all diagnosed tumors. Malignant primary spinal axis tumors comprise about 65% of all spinal axis tumors. However, most spinal axis tumors result from **metastasis**, or spreading, of other types of cancer to the

spinal axis. Other cancers that can spread to the spinal axis include head and neck cancer, **thyroid cancer**, skin cancer, **prostate cancer**, lung cancer, **breast cancer**, and others. The American Cancer Society estimates that brain and spinal cord cancers (primary only) represent approximately 1.4% of all cancers and 2.4% of all cancer-related deaths, but separate statistics for spinal cord cancers only are unavailable.

Half of all spinal axis tumors occur in the thoracic, or chest, region as opposed to the neck (cervical) or lower back (lumbar) region.

Spinal axis tumors occur with equal frequency in members of all races and ethnic groups. There does not appear to be any relationship between spinal axis tumors and any geographic region. Males and females are affected in equal numbers by spinal axis tumors.

Causes and symptoms

The cause, or causes, of primary spinal axis tumors are not known. The cause of metastatic spinal axis tumors is the originating cancer in another part of the body.

The symptoms of spinal axis tumors are the result of increased pressure on the nerves of the spine. These symptoms include:

- constant, severe, burning or aching pain
- numbness of the skin or decreased temperature sensation
- muscle weakness, wasting, or even paralysis
- problems with bladder and bowel control
- muscle spasticity or problems in walking normally

The location of the tumor determines where the symptoms are most noticeable. A tumor in the cervical region can cause symptoms in the neck or arms, while a tumor in the thoracic region may cause chest pain. A tumor in the lumbar region can result in observable symptoms in the back, bladder and bowel, and legs.

Diagnosis

The diagnosis of spinal axis tumors begins with a medical history and physical examination when the patient brings his or her symptoms to the doctor's attention. The diagnosis may be difficult to make due to the similarity of tumor symptoms to those caused by disc herniation or other spinal cord injuries.

If the doctor suspects a spinal axis tumor may be present, further diagnostic tests are ordered. These tests are performed by a neurological specialist. Imaging tests that may be ordered include:

- magnetic resonance imaging (MRI)
- computed tomography (CT)
- bone scan
- spinal tap and myelogram, a specialized x-ray technique

KEY TERMS

Astrocytoma—A tomor that begins in the brain or spinal cord in cells called astrocytes.

Chordoma—A type of bone cancer.

Dura mater—The tough membrane that encases the nerves of the spinal cord.

Ependymoma—A tumor that begins in the tissue that lines the central canal of the spinal cord and the ventricles of the brain. About 85% of these tumors are benign.

Hemangioblastoma—A tumor composed of capillaries and disorganized clumps of capillary cells or angioblasts.

Hemangioma—A benign tumor consisting of a mass of blood vessels.

Meningioma—A tumor that occurs in the meninges, the membranes that cover the brain and spinal cord. Meningiomas usually grow slowly and primarily affect adults.

Metastasic tumor—A tumor that results from the spreading of one type of cancer to other parts of the body.

Neurofibroma—A fibrous tumor of nerve tissue.

Osteoblastoma—A benign tumor that most frequently occurs in the vertebrae, leg bones, or arm bones of children and young adults.

Osteoma—A usually benign tumor of bone tissue.

Spinal cord—The bundle of nerves that runs inside the backbone.

Treatment team

Treatment of any primary central nervous system tumor, including spinal axis tumors, is different from treating tumors in other parts of the body. Spinal cord surgery requires much more precision than most other surgeries. Also, the thoracic area, where the majority of spinal axis tumors are located, is highly sensitive to radiation. The most up-to-date treatment opportunities are available from experienced, multi-disciplinary medical professional teams made up of doctors, nurses, and

technologists who specialize in cancer (oncology), neurosurgery, medical imaging, drug or **radiation therapy**, and anesthesiology.

Clinical staging, treatments, and prognosis

Malignant tumors of the spinal axis may spread (metastasize) to other parts of the central nervous system, but almost never spread to other parts of the body. As of mid-2001, there is no staging system for spinal axis tumors. The most important factors in determining prognosis for individuals with these tumors are the type of cell involved (eg. astrocyte, ependyma, etc.) and the grade of the tumor (an indicator of the aggressiveness of the tumor cells). Grade I tumors have cells that are not malignant and are nearly normal in appearance. Grade II tumors have cells that appear to be slightly abnormal. Grade III tumors have cells that are malignant and clearly abnormal. Grade IV tumors contain fast-spreading and abnormal cells. In general, the survival rate for some types of spinal cord tumors, such as extradural tumors and low-grade astrocytomas, is better than for other types, such as ependymomas.

The treatment of spinal axis tumors depends on the location of the tumor and the severity of the symptoms. Many spinal axis tumors can be treated by surgical removal of the tumor. Medical advances in surgical techniques, such as microsurgery and laser surgery, have greatly improved the success rate of spinal cord surgeries.

In some instances of spinal axis tumors, the tumor is inoperable. Patients with inoperable spinal axis tumors are generally treated with radiation therapies.

Other treatments may include the use of steroids to reduce swelling and pressure on the spinal cord, surgical decompression and fusion of the spine, and **chemotherapy** in selected cases. These may be the only treatments used if the spinal axis tumor is due to the metastasis of another primary cancer.

Prevention

Because the causes of spinal axis tumors are not known, there are no known preventative measures.

Special concerns

If left untreated, spinal axis tumors can cause loss of muscle function up to and including paralysis. This makes the proper diagnosis of spinal axis tumors important.

See also Astrocytoma; Brain and central nervous system tumors; Chordoma; Ependymoma.

QUESTIONS TO ASK THE DOCTOR

- Which type of spinal axis tumor do I have?
- Is my tumor operable?

Resources

ORGANIZATIONS

The Brain Tumor Society. 124 Watertown Street, Suite 3-H, Watertown, MA 02472. (617) 924-9997. Fax: (617) 924-9998. <http://www.tbts.org/>.

National Brain Tumor Foundation. 785 Market Street, Suite 1600, San Francisco, CA 94103. (415) 284-0208. <http://www.braintumor.org/>.

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Spinal cord compression

Description

In order to understand spinal cord compression, it is useful to understand the structure of the spinal cord and to understand the difference between the spinal cord and the vertebral column. The vertebral column includes the bony structure surrounding the spinal cord and the spinal cord itself. Also an important part of the vertebral column, the intervertebral disks, are found between vertebrae. They act as shock absorbers. The spinal cord, however, is the series of nerves that runs down the hollow part of the vertebrae. Thus, the bony vertebrae and shock-absorbing disks protect the spinal cord from physical damage and compression.

Spinal cord compression occurs when something presses down with sufficient force on the nerves within the spinal cord so that they lose their ability to function properly. Although trauma, degenerative back disease, and genetic disorders can cause pressure on the spinal

cord, the term spinal cord compression is usually reserved for cases in which the presence of a tumor results in pressure on the spinal cord. The tumor may originate in a number of areas and either directly or indirectly put pressure on the cord.

The spinal cord is a series of nerves bundled together that are responsible for most functions of the body, including, but not limited to, the "fight or flight" response, the movement of arms and legs, and feeling below the neck. Each nerve is responsible for different functions, such as movement, and each has a different position within the structure of the spinal cord. Thus, depending on which angle the spinal cord is compressed from, a person could experience numbness versus a loss of the ability to control muscles (often seen as an odd limp), depending on which area is compressed.

Not only do the different nerve clusters of the spinal cord have different functions, but each has nerves branching off from the spinal cord at many levels. Each of these branches controls different parts of the body. For example, nerves branching off the spinal cord in the low back control movement of the legs, and nerves branching off the spinal cord at the level of the neck are responsible for most of the movements of the arm. Thus, compression of the spinal cord at different levels can result in very different symptoms.

Vertebrae are, in order, divided into cervical, thoracic, lumbar, and sacral sections. The cervical vertebrae correspond to the neck, the thoracic vertebrae correspond to most of the torso, the lumbar vertebrae are found in the low back, and the sacral vertebrae correspond to the area of the buttocks. There are seven cervical, twelve thoracic, five lumbar, and five sacral vertebrae (although the sacrum is one bony structure and contains no intervertebral disks). The level of compression is indicated by using the first letter of the type of vertebra and then the number of the vertebra within the group. The topmost vertebrae are numbered lowest, so the first cervical vertebra is the vertebra closest to the head, and is known as C1. C7 is the cervical vertebra furthest down the spine. Compression of the spinal cord in this region would be known as compression at C7. The closer the compression is to the head, the more symptoms the patient is likely to have, since compression of the spinal cord affects all the levels of nerves below the area of compression that are part of the same nerve branch. For example, if movement were affected at C2 and below, a person would have difficulty using both arms and legs, whereas compression at T12 might result in just difficulty using the legs.

Importantly, the first symptom patients usually display prior to actual spinal cord compression is pain, especially pain that is not relieved by lying down, and which has lasted one month or more. This kind of pain should be sufficient to suspect imminent spinal cord compression due to cancerous causes. Also, there may be damage to nerve roots at the level of compression that can lead to symptoms in other parts of the body. For example, if the cord compression is in the lower part of the spine, then parts of the legs may be affected with numbness, tingling and loss of power and movement. Similarly, if the problem lies in the upper part of the spinal column, there may be a loss of power and sensation in parts of the arms or hands. If the cord compression becomes more severe, it can affect lower muscle functions such as bowel and bladder.

Causes

The most common cause of cancerous spinal cord compression is a vertebral **metastasis**. A metastasis is a cancerous lesion that arises from another tumor somewhere else in the body. Vertebral metastases account for 85% of cases of spinal cord compression, and 70% of those metastases occur in the thoracic vertebrae. About 5% to 10% of patients with cancer will develop metastases to the spinal cord. Tumors may also grow from the nerves themselves, from the connective tissue surrounding the nerves, or, rarely, from the bony vertebrae themselves. Tumors that grow from outside the vertebral column may cause pressure by either growing into the hollow space in the vertebral column or by pressuring the vertebrae into an abnormal conformation. More rarely, tumors in the vertebrae may cause compression indirectly by causing the vertebrae to collapse. Tumors that originate in the spinal cord or in the connective tissue overlying the spinal cord cause direct pressure because there is a limited area in which they can grow before impinging on the cord directly.

Treatments

If symptoms develop, prompt diagnosis and rapid treatment are crucial in order to avoid any permanent damage to the sensitive nerve tissue of the spinal cord. Usually, **magnetic resonance imaging** (MRI) or **computed tomography** (CT) scans will be performed to confirm cord compression and fully define the level and extent of the lesion. High-dose **corticosteroids** (oral or IV **dexamethasone**) may be promptly administered in order to reduce inflammation and pressure.

The goal of therapy for spinal cord compression includes pain control, avoidance of complications, preserving or improving neurologic functions, or reversing impaired neurologic functions. Treatment usually involves treatment of the underlying tumor. For most patients with cancer-induced compression, **radiation therapy** is the treatment of choice. However, if radiation

KEY TERMS

Neurologic—Pertaining to the nervous system.

Spinal cord—The name given to the series of nerves which travel down the vertebral column and govern most of the functions of the body, such as movement and sensation.

Vertebral column—The vertebral column is the bony structure made up of vertebra and intervertebral disks whose primary function is to protect the spinal cord.

therapy is unavailable or if neurologic signs worsen despite medical therapy, surgical decompression should be performed. Surgery is also indicated when a **biopsy** is needed, when the spine is unstable, when tumors have recurred after radiation therapy, or when any abscess is present. Finally, in some tumors known to be highly chemoresponsive, **chemotherapy** alone or in combination with other modalities may be used.

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Splenectomy

Definition

Splenectomy is the surgical removal of the spleen, which is an organ that is part of the lymphatic system. The spleen is a dark purple, bean-shaped organ located in the upper left side of the abdomen, just behind the bottom of the rib cage. In adults, the spleen is about 4.8 × 2.8 × 1.6 in in size, and weighs about 4 or 5 oz. (It measures 12 × 7 × 4 cm, and weighs between 113 and 141 grams.) Its functions include: playing a role in the immune system, filtering foreign substances from the blood, removing worn-out blood cells from the blood, regulating blood flow to the liver, and sometimes storing blood cells. The storage of blood cells is called sequestration. In healthy adults, about 30% of blood platelets are sequestered in the spleen.

Purpose

Splenectomies are performed for a variety of different reasons and with different degrees of urgency. Most splenectomies are done after the patient has been diagnosed with hypersplenism. Hypersplenism is not a specific disease but a group of symptoms, or a syndrome, that can be produced by a number of different disorders. Hypersplenism is characterized by enlargement of the spleen (splenomegaly), defects in the blood cells, and an abnormally high turnover of blood cells. It is almost always associated with splenomegaly caused by specific disorders such as cirrhosis of the liver or certain cancers, such as leukemia or lymphomas (both Hodgkin's and non-Hodgkin's). Because serious consequences may result from removal of immune system organs such as the spleen, the decision to perform a splenectomy depends on the severity and prognosis of the disease or condition causing the hypersplenism.

Splenectomy always necessary

There are two diseases for which splenectomy is the only treatment—primary cancers of the spleen and a blood disorder called hereditary spherocytosis (HS). In HS, the absence of a specific protein in the red blood cell membrane leads to the formation of relatively fragile cells that are easily damaged when they pass through the spleen. The cell destruction does not occur elsewhere in the body and ends when the spleen is removed. HS can appear at any age, even in newborns, although doctors prefer to put off removing the spleen until the child is five or six years old.

Splenectomy usually necessary

There are some disorders in which splenectomy is usually recommended. They include:

- Immune (idiopathic) thrombocytopenic purpura (ITP). ITP is a disease involving platelet destruction. Splenectomy has been regarded as the definitive treatment for this disease and is effective in about 70% of chronic ITP cases. More recently, however, the introduction of new drugs in the treatment of ITP has reopened the question as to whether splenectomy is always the best treatment option.
- Trauma. The spleen can be ruptured by blunt as well as penetrating injuries to the chest or abdomen. Car accidents are the most common cause of blunt traumatic

injury to the spleen. Occasionally, the spleen is injured during an operation within the abdomen. Sometimes, the spleen can be repaired (splenorrhaphy) rather than removed.

- Abscesses in the spleen. These are relatively uncommon but have a high mortality rate.
- Rupture of the splenic artery. Rupture sometimes occurs as a complication of pregnancy.
- Hereditary elliptocytosis. This is a relatively rare disorder. It is similar to HS in that it is characterized by red blood cells with defective membranes that are destroyed by the spleen.

Due to more sophisticated imaging techniques, nonoperative splenic preservation is becoming more common for injuries due to splenic trauma. Splenectomy should be avoided whenever possible as the advantages of splenic preservation have been well established. Specifically, splenectomy increases the risks of postoperative and long-term infection, and the procedure is associated with excessive transfusion requirements.

Splenectomy sometimes necessary

In other disorders, the spleen may or may not be removed.

- Hodgkin's disease, a serious form of cancer that causes lymph nodes to enlarge and causes the immune system to malfunction. Treatments such as radiation, **chemotherapy**, and surgical removal of the spleen can exacerbate this malfunction, increasing the likelihood of infection. Splenectomy is sometimes performed in order to find out how far the disease has progressed. However, splenectomy has been shown to increase the risk of secondary **acute leukemia** in patients with Hodgkin's disease.
- Hairy cell leukemia. Patients may suffer discomfort due to a very enlarged spleen caused by leukemia cells growing in the spleen. Splenectomy was once the only treatment for this disease; but due to the complications associated with splenectomy (low blood cell counts, **fatigue**, frequent infections, and easy bleeding or bruising), physicians are now more often recommending chemotherapy.
- Chronic myeloid disorders. These disorders include chronic myelocytic leukemia, polycythemia vera, essential thrombocythemia, and agnogenic myeloid metaplasia (**myelofibrosis**); they enlarge the spleen to various degrees. In early stages of chronic myelocytic leukemia, splenectomy does not provide much benefit.
- Myelofibrosis. Myelofibrosis is a disorder in which bone marrow is replaced by fibrous tissue. It produces severe and painful splenomegaly. Splenectomy does not cure myelofibrosis but may be performed to relieve pain caused by the swollen spleen.
- Thrombotic thrombocytopenic purpura (TTP). TTP is a rare disorder marked by **fever**, kidney failure, and an abnormal decrease in the number of platelets. Splenectomy is one part of treatment for TTP.
- Autoimmune hemolytic disorders. These disorders may appear in patients of any age but are most common in patients over 50. The red blood cells are destroyed by antibodies produced by the patient's own body (autoantibodies).
- Thalassemia. Thalassemia is a hereditary form of **anemia** that is most common in people of Mediterranean origin. Splenectomy is sometimes performed if the patient's spleen has become painfully enlarged.

Precautions

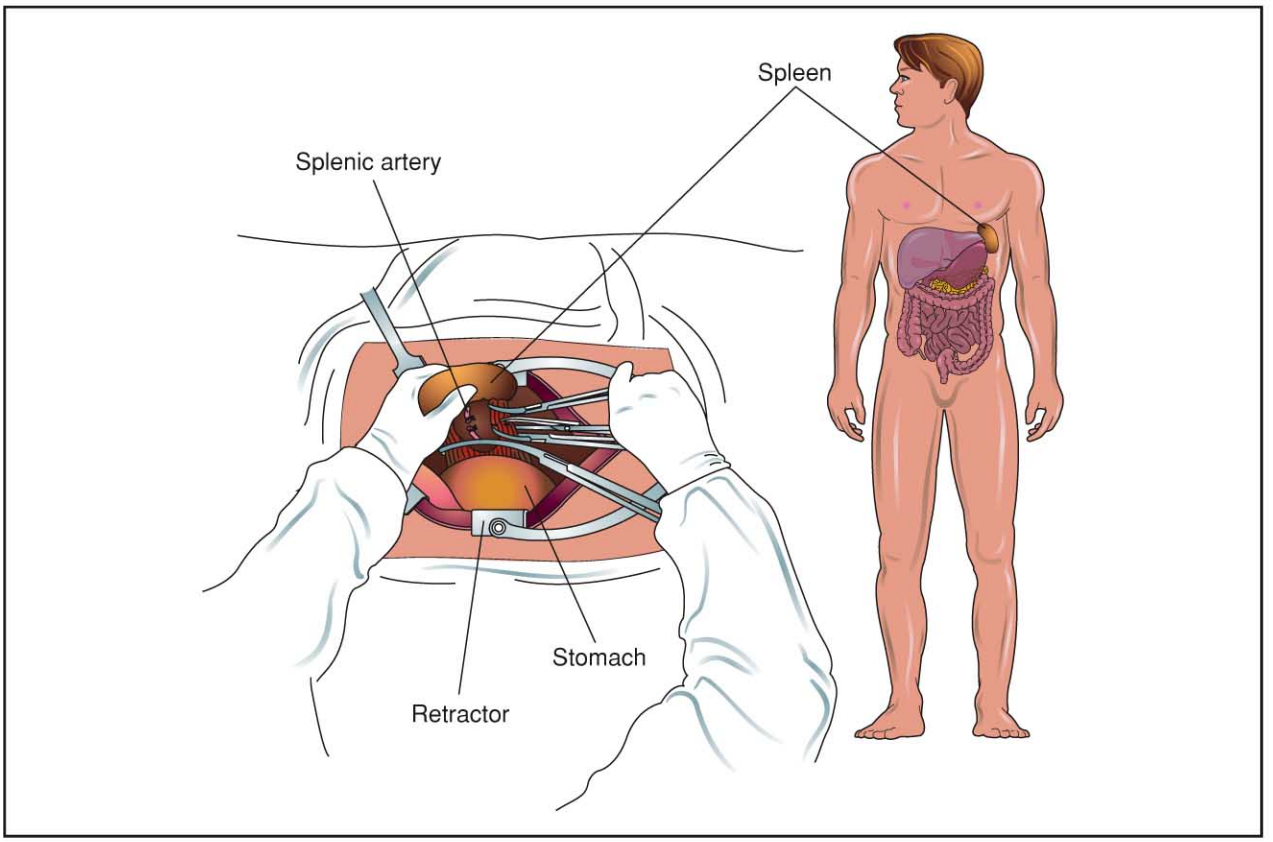
Patients should be carefully assessed regarding the need for a splenectomy. Because of the spleen's role in protecting against infection, it should not be removed unless necessary. The operation is relatively safe for young and middle-aged adults. Older adults, especially those with cardiac or pulmonary disease, are more vulnerable to post-surgical infections. Thromboembolism following splenectomy is another complication for this patient group, which has about 10% mortality following the surgery. Splenectomies are performed in children only when the benefits outweigh the risks.

The most important part of the assessment is the measurement of splenomegaly. The normal spleen cannot be felt when the doctor examines the patient's abdomen. A spleen that is large enough to be felt indicates splenomegaly. In some cases the doctor will hear a dull sound when he or she thumps (percusses) the patient's abdomen near the ribs on the left side. **Imaging studies** that can be used to demonstrate splenomegaly include ultrasound tests, technetium-99m sulfur colloid imaging, and **computed tomography** (CT) scans. The rate of platelet or red blood cell destruction by the spleen can be measured by tagging blood cells with radioactive chromium or platelets with radioactive indium.

Description

Complete splenectomy

REMOVAL OF ENLARGED SPLEEN Splenectomy is performed under general anesthesia. The most common technique is used to remove greatly enlarged spleens. After the surgeon makes a cut (incision) in the abdomen, the artery to the spleen is tied to prevent blood loss and reduce the spleen's size. It also helps prevent further sequestration



Splenectomy is the surgical removal of the spleen. This procedure is performed as a last resort in most diseases involving the spleen. In some cases, such as in many types of cancer, splenectomy does not cure the condition causing the splenomegaly—it only relieves the symptoms from the enlarged spleen. *(Illustration by Electronic Illustrators Group.)*

of blood cells. The surgeon detaches the ligaments holding the spleen in place and removes it. In many cases, tissue samples will be sent to a laboratory for analysis.

REMOVAL OF RUPTURED SPLEEN When the spleen has been ruptured by trauma, the surgeon approaches the organ from its underside and fastens the splenic artery.

In some cases, the doctor may prefer conservative (non-surgical) management of a ruptured spleen, most often when the patient's blood pressure is stable and there are no signs of other abdominal injuries. In the case of multiple abdominal trauma, however, the spleen is usually removed.

Partial splenectomy

In some cases the surgeon removes only part of the spleen. This procedure is considered by some to be a useful compromise that reduces pain from an enlarged spleen while leaving the patient less vulnerable to infection.

Laparoscopic splenectomy

Laparoscopic splenectomy, or removal of the spleen through several small incisions, has been more frequently used in recent years. Laparoscopic surgery involves the use of surgical instruments, with the assistance of a tiny camera and video monitor. Laparoscopic procedures reduce the length of hospital stay, the level of post-operative pain, and the risk of infection. They also leave smaller scars. Laparoscopic splenectomy is not, however, the best option for many patients.

A laparoscopic splenectomy using a hanger wall-lifting procedure may provide a better technique and can avoid the usual complications associated with pneumoperitoneum. The patient's left lower chest and left abdominal wall are lifted by three wires in two directions, left laterally and vertical to the abdominal wall.

Laparoscopic splenectomy is gaining increased acceptance in the early 2000s as an alternative to open splenectomy for a wide variety of disorders, although splenomegaly still presents an obstacle to laparoscopic splenectomy; massive splenomegaly has been considered a contraindication. In patients with enlarged spleens, however, laparoscopic splenectomy is associated with less morbidity, decreased transfusion rates, and shorter hospital stays than when the open approach is

used. Patients with enlarged spleens usually have more severe hematologic diseases related to greater morbidity; therefore, laparoscopic splenectomy has potential advantages.

The most frequent serious complication following laparoscopic splenectomy is damage to the pancreas. Application of a hydrogel sealant to the pancreas during surgery, however, appears to significantly reduce the risk of leakage from the pancreas.

Splenic embolization

Splenic embolization is an alternative to splenectomy that is used in some patients who are poor surgical risks. Embolization involves plugging or blocking the splenic artery to shrink the size of the spleen. The substances that are injected during this procedure include polyvinyl alcohol foam, polystyrene, and silicone. Embolization is a technique that needs further study and refinement.

Preparation

Preoperative preparation for nonemergency splenectomy includes:

- correction of abnormalities of blood clotting and the number of red blood cells and/or platelets
- treatment of any infections
- Control of immune reactions. Patients are usually given protective vaccinations about a month before surgery. The most common **vaccines** used are Pneumovax or Pnu-Imune 23 (against Pneumococcal infections) and Menomune-A/C/Y/W-135 (against meningococcal infections).

Aftercare

Immediately following surgery, patients should follow instructions and take all medications intended to prevent infection. Blood transfusions may be indicated for some patients to replace defective blood cells. The most important part of aftercare, however, is long-term caution regarding vulnerability to infection. Patients should see their doctor at once if they have a fever or any other sign of infection, and avoid travel to areas where exposure to malaria or similar diseases is likely. Children with splenectomies may be kept on antibiotic therapy until they are 16 years old. All patients can be given a booster dose of pneumococcal vaccine five to ten years after splenectomy.

Risks

The chief risk following splenectomy is overwhelmingly bacterial infection, or postsplenectomy sepsis. This vulnerability results from the body's decreased ability to clear bacteria from the blood, and lowered levels of a protein in blood plasma that helps to fight viruses (immunoglobulin M). The risk of dying from infection after splenectomy is highest in children, especially in the first two years after surgery. The risk of postsplenectomy sepsis can be reduced by vaccinations before the operation. Some doctors also recommend a two-year course of penicillin following splenectomy or long-term treatment with ampicillin.

KEY TERMS

Embolization—An alternative to splenectomy that involves injecting silicone or similar substances into the splenic artery to shrink the size of the spleen.

Hereditary spherocytosis (HS)—A blood disorder in which the red blood cells are relatively fragile and are damaged or destroyed when they pass through the spleen. Splenectomy is the only treatment for HS.

Hypersplenism—A syndrome marked by enlargement of the spleen, defects in one or more types of blood cells, and a high turnover of blood cells.

Immune or idiopathic thrombocytopenic purpura (ITP)—A blood disease that results in destruction of platelets, which are blood cells involved in clotting.

Laparoscope—An instrument used to view the abdominal cavity through a small incision and perform surgery on a small area, such as the spleen.

Pneumovax—A vaccine that is given to splenectomy patients to protect them against bacterial infections. Other vaccines include Pnu-Imune and Menomune.

Sepsis—A generalized infection of the body, most often caused by bacteria.

Sequestration—A process in which the spleen withdraws some normal blood cells from circulation and holds them in case the body needs extra blood in an emergency. In hypersplenism, the spleen sequesters too many blood cells.

Splenomegaly—Abnormal enlargement of the spleen.

Thromboembolism—A clot in the blood that forms and blocks a blood vessel. It can lead to infarction, or death of the surrounding tissue due to lack of blood supply.

Other risks following splenectomy include inflammation of the pancreas and collapse of the lungs. In some cases, splenectomy does not address the underlying causes of splenomegaly or other conditions. Excessive bleeding after the operation is an additional possible complication, particularly for ITP patients. Infection immediately following surgery may also occur.

Normal results

Results depend on the reason for the operation. In blood disorders, the splenectomy will remove the cause of the blood cell destruction. Normal results for patients with an enlarged spleen are relief of pain and of the complications of splenomegaly. It is not always possible, however, to predict which patients will respond well or to what degree.

See also Infection and sepsis.

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Leukaemia Research Fund. 43 Great Ormond St., London WCIN 3JJ. <http://dspace.dial.pipex.com/lrf-//>.

National Heart, Lung and Blood Institute. Building 31, Room 4A21, Bethesda, MD 20892. (301)496-4236. <http://www.nhlbi.nih.gov>.

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Squamous cell carcinoma of the skin

Definition

A squamous cell carcinoma is a skin cancer that originates from squamous keratinocytes in the epidermis, the top layer of the skin. *Squamous* is a term that indicates a surface with a scaly nature.

Description

Squamous keratinocytes are flattened unpigmented skin cells in the middle of the epidermis. When they become cancerous, these cells invade the dermis (the layer of skin just below the epidermis) and spread out into the normal skin. They become visible as a small growth or area of change in the skin's appearance.

Most squamous cell carcinomas appear on areas that have been exposed to the sun: the head and neck, forearms, backs of the hands, upper part of the torso, and lower legs. Many develop in precancerous patches called actinic keratoses. Actinic keratoses are rough, scaly patches on the skin that usually start to show up in middle age. They are associated with a lifetime's exposure to the sun. Estimates of the chance that an actinic keratosis will turn into a squamous cell carcinoma vary from 0.24% to 20%.

Squamous cell carcinomas can also originate in old scars and burns, long-standing sores, and other areas of chronic skin irritation. These tumors tend to be more dangerous than those that arise in actinic keratoses.

The least dangerous type of squamous cell carcinoma is called **Bowen's disease**, intraepithelial squamous cell carcinoma, or squamous cell carcinoma *in situ*. Bowen's disease can show up anywhere on the skin, but it is especially common on the head and neck. This cancer usually grows slowly; but may evolve into a more serious, spreading form if it is not removed.

Other types of squamous cell carcinomas grow fairly quickly and can develop within a few months. These tumors may spread in the skin along the blood vessels, nerves, and muscles. They can also metastasize, or spread to other areas. On the average, 2–6% of squamous cell carcinomas metastasize, but the rate varies with the tumor site. At least 95% of the tumors that originate in actinic keratoses remain in the skin; but up to 38% of the cancers from scars are metastatic. **Metastasis** is also more likely when the cancer originates on the ear, lip, or genitalia, is large or deep, or develops in someone with a severely suppressed immune system. Cancers that regrow after treatment, and tumors that spread along the nerves are particularly dangerous.

Demographics

Squamous cell carcinoma is the second most common type of skin cancer in North America. There are between 80,000 and 100,000 cases diagnosed each year in the United States.

Squamous cell carcinomas are more common in the older adult population rather than the young. Overall, the chance of developing one is about 7%–11%. The likelihood increases with exposure to the sun, and is greatest for fair-skinned individuals who tan poorly. Living near the equator, where ultraviolet light is more intense, also increases the risk. A weakened immune system— for instance, from an organ transplant, or AIDS—can also increase the risk of developing a squamous cell carcinoma by a factor of 5 to 250.

Squamous cell carcinomas tend to be most dangerous in individuals with dark skin. The mortality rate for African-Americans with squamous cell carcinomas is 17–24%, much higher than the 2% death rate for white males with nonmelanoma skin cancer. One reason for this disparity is that the cancers that develop in dark skin are more likely to come from old scars and burns than from actinic keratoses.

Causes and symptoms

Squamous cell carcinoma is caused by genetic damage to a skin cell. A number of factors can increase the risk that this will happen, but the exact cause is rarely known.

Any of the following changes may be a warning sign that an actinic keratosis is developing into a squamous cell carcinoma:

- pain
- increased redness
- sores or bleeding
- hardening or thickening
- increased size

Most squamous cell carcinomas begin as a small red bump on the skin. More advanced squamous cell carcinomas have the following characteristics:

- a few millimeters to a few centimeters in diameter
- reddish-brown, flesh-colored, pink, or red
- bumpy or flat
- sharp, irregular edges in Bowen's disease; others may have no definite edge
- may be crusted or scaly
- may contain bleeding sores

Diagnosis

Squamous cell carcinomas are usually diagnosed with a skin **biopsy** taken in the doctor's office. This is generally a brief, simple procedure. After numbing the skin with an injection of local anesthetic, the doctor snips out the tumor or a piece of it. This skin sample is sent to a pathologist to be read. It can take up to a week for the biopsy results to come back. Squamous cell carcinomas are graded into categories of one through four. The grading is based on how deeply the tumor penetrates in the skin and how abnormal its cells are. Higher grades are more serious.

Treatment team

Primary care physicians remove some squamous cell carcinomas; other cancers, including larger or more complicated tumors, may be referred to a dermatologist. The services of a plastic surgeon are occasionally necessary. Metastatic tumors are often treated by an oncologist, surgeons, specially trained nurses, and specialists in radiation treatment.

Clinical staging, treatments, and prognosis

Staging

In stage 0 (Bowen's disease), the cancer is very small and has not yet spread from the epidermis to the dermis.

In stage I, the cancer is less than 2 cm (0.8 inches) in diameter. No cancer cells can be found in lymph nodes or other internal organs.

In stage II, the cancer is more than 2 cm (0.8 inches) in diameter. No cancer cells can be found in lymph nodes or other internal organs.

In stage III, cancer cells have been found in nearby lymph nodes or in the bone, muscle, or cartilage beneath the skin.

A stage IV cancer can be any size. In this stage, cancer cells have been discovered in internal organs that are distant from the skin. Squamous cell carcinomas tend to spread to nearby lymph nodes, the liver, and the lungs.

Treatment

The treatment options for a squamous cell carcinoma depend on the size of the tumor, its location, and the likelihood that it will spread aggressively or metastasize. All of the treatments described below generally have cure rates of approximately 90% to 99% for small, localized cancers. The five-year cure rates are highest with Moh's surgery, also called Mohs micrographic surgery.

One option is conventional surgery. The doctor numbs the area with an injection of local anesthetic, then cuts out the tumor and a small margin of normal skin around it. The wound is closed with a few stitches. One advantage of conventional surgery is that the wound usually heals quickly. Another benefit is that the complete cancer can be sent to a pathologist for evaluation. If cancer cells are found in the skin around the tumor, additional treatments can be done.

Laser surgery may be an alternative. A disadvantage to laser surgery is that the wounds from some lasers heal more slowly than cuts from a scalpel. The advantage is that bleeding is minimal.

Another option is Moh's micrographic surgery. This technique is a variation of conventional surgery. In this procedure, the surgeon examines each piece of skin under the microscope as it is removed. If any cancer cells remain, another slice is taken from that area and checked. These steps are repeated until the edges of the wound are clear of tumor cells, then the wound is closed. The advantage to this technique is that all of the visible cancer cells are removed but as much normal skin as possible is spared. Mohs surgery is often used for larger or higher risk tumors and when cosmetic considerations are important. The main disadvantage is that it takes much longer than conventional surgery and requires a specially trained surgeon.

In cryosurgery, liquid nitrogen is used to freeze the tumor and destroy it. This treatment is another type of blind destruction; there is no skin sample to make sure the cancer cells have all been killed. Patients report swelling and pain after cryosurgery, and a wound appears a few days later where the cells were destroyed. Healing takes about four to six weeks. When the site heals, it has usually lost its normal pigment. There is a risk of nerve damage with this technique. Cryosurgery is generally used only for small cancers in stage 0 and stage I.

In electro dessication and curettage, the physician scoops out the cancer cells with a spoon-shaped instrument called a curette. After most of the tumor is gone, the rest is destroyed with heat from an electrical current. The wound is left open to heal like an abrasion. It leaks fluid, crusts over, and heals during the next two to six weeks. This method is generally used only for the smallest squamous cell carcinomas (stage 0 and stage I). One disadvantage is that there is no skin sample to confirm that the tumor is completely gone. The electrical current used during this surgery can interfere with some pacemakers.

Some cases of Bowen's disease can be treated by applying a lotion containing 5-fluorouracil (fluorouracil or 5-FU) for several weeks. This treatment usually gives good cosmetic results. The side effects from 5-fluorouracil include allergies to the ingredients, infections, redness, peeling, and crusting, sensitivity to the sun, and changes in skin color. The main disadvantage to this treatment is that the drug cannot penetrate very far and cancer cells in the deeper parts of the tumor may not be destroyed.

Radiation therapy is sometimes used for squamous cell carcinomas, especially when the tumor is at a site where surgery would be difficult or remove a sizeable amount of tissue. This treatment is sometimes combined with surgery for cancers that have metastasized or are likely to. One disadvantage is that tumors returning after radiation tend to grow more quickly than the original cancer. In addition, x rays may promote new skin cancers. The cosmetic results are usually good. In some cases the skin may lose a little pigment, or develop spider veins. Some doctors reserve radiation treatment for those over 60. One drawback of radiation therapy for squamous cell carcinomas in or near the mouth is that the radiation may cause the tissues inside the mouth to break down.

Chemotherapy is often added to surgery or radiation for stage IV cancers. Retinoids and interferon are experimental treatments that may be helpful.

Prognosis

Because many squamous cell carcinomas are not staged, precise five-year survival rates for each stage are not available. In general, the prognosis is very good for small squamous cell carcinomas that originate in actinic

KEY TERMS

Actinic keratosis (plural actinic keratoses)—A rough, dry, scaly patch on the skin associated with sun exposure.

Albinism—A genetic disease characterized by the absence of the normal skin pigment, melanin.

Antioxidant—A substance that can neutralize free radicals. Free radicals are damaging molecules formed from oxygen. Antioxidant vitamins include vitamin E, C, and beta-carotene, a form of vitamin A.

Biopsy—A sample of an organ taken to look for abnormalities. Also, the technique used to take such samples.

Chronic—Long-standing.

Dermis—A layer of skin sandwiched between the epidermis and the fat under the skin. It contains the blood vessels, nerves, sweat glands, and hair follicles.

Epidermis—The thin layer of skin cells at the surface of the skin.

Fluorouracil—A cancer drug.

Interferon alpha—A chemical made naturally by the immune system and also manufactured as a drug.

Local anesthetic—A liquid used to numb a small area of the skin.

Lymph node—A small organ full of immune cells, found in clusters throughout the body. Lymph nodes are where reactions to infections usually begin.

Nonmelanoma skin cancer—A squamous cell carcinoma or basal cell carcinoma.

Nonsteroidal anti-inflammatory drugs (NSAIDS)—A class of drugs that suppresses inflammation. Includes a wide variety of drugs, including aspirin.

Papillomavirus—A member of a group of viruses associated with warts and cervical cancer.

Pathologist—A doctor who specializes in examining cells and other parts of the body for abnormalities.

Precancerous—Abnormal and with a high probability of turning into cancer, but not yet a cancer.

Oncologist—A doctor who specializes in the treatment of cancer.

Retinoids—A class of drugs related to vitamin A.

Selenium—A mineral needed in extremely small quantities by the body. Large amounts can be very toxic.

Xeroderma pigmentosum—A genetic disease characterized by the inability to repair damaged DNA. Individuals with this disease develop an excessive number of skin cancers.

keratoses. However, cancers that were not completely destroyed may regrow. Tumors can redevelop in the scar from the surgery, on the edges of the surgery site, or deep in the skin. Larger or higher-risk tumors, cancers that regrow after treatment, and tumors that have invaded local tissues or metastasized are more difficult to cure. Most metastases show up within the first two years after a skin tumor has been removed. The five-year survival rate for metastatic cancers is 34%.

Alternative and complementary therapies

Alternative treatments for squamous cell carcinoma usually attempt to prevent rather than treat this cancer. Options being tested include antioxidant **vitamins**, minerals, and green tea extracts.

Coping with cancer treatment

Most squamous cell carcinomas are removed with techniques that cause few, if any, lasting side effects. Patients who have cosmetic concerns may wish to discuss them with their doctors.

Clinical trials

The medical community considers the following treatments to be experimental.

Clinical trials are testing whether interferon alpha, injected into the tumor, can destroy some squamous cell carcinomas. An early report from a combination of interferon alpha and retinoids is promising.

Ongoing trials are also evaluating whether small squamous cell carcinomas can be cured with photodynamic laser therapy. In this technique, a dye activated by laser light destroys the cancer. This dye is spread onto the skin, injected, or drunk. During a waiting period, normal cells clear the dye, then a laser activates the remainder. As of 2001, this technique was only useful for cancers very near the surface of the skin. One side effect after treatment is a period of excessive sun-sensitivity.

Other clinical trials are testing whether retinoids spread onto the skin can prevent or treat squamous cell carcinoma.

Another new experimental approach to squamous cell carcinoma is gene therapy. Researchers in Texas

reported in 2003 on a Phase III investigation that uses an adenovirus as a vector to carry an altered p53 gene into the cancerous squamous cells. The function of the p53 gene is to maintain the structure of the cell's DNA and to induce the cell to die if its DNA is damaged beyond repair. Phase I and phase II trials have indicated that this approach to treatment has lengthened the survival time in patients with recurrent squamous cell carcinoma.

Prevention

The most important risk factor for squamous cell carcinoma is exposure to the sun (or other source of ultraviolet light) combined with a lighter complexion and inability to tan. Other risk factors include:

- increasing age
- actinic keratoses
- a previous skin cancer
- exposure to arsenic or the chemicals in coal tars
- radiation treatments
- treatment with psoralen and ultraviolet light for psoriasis
- chronic skin damage such as burn scars and ulcers
- infection with some varieties of human papillomavirus
- genetic disorders such as xeroderma pigmentosum and albinism
- a weakened immune system

Most people will receive 80% of their lifetime exposure to the sun before they reach the age of 20. For this reason, prevention should start during childhood and adolescence. Some important steps to prevent squamous cell carcinoma, as well as other skin cancers include:

- Wear protective clothing and a wide-brimmed hat in the sun.
- Stay out of the sun from 10 A.M. to 4 P.M..
- Use a sunscreen that has a sun protection factor (SPF) of at least 15.
- Avoid suntanning booths.

Drugs related to vitamin A (including beta-carotene and retinoids), vitamin E, nonsteroidal anti-inflammatory drugs (NSAIDS), and selenium might be able to prevent some skin cancers. In 2001, their effectiveness was still in question.

Special concerns

Because many squamous cell carcinomas are found on the face and neck, cosmetic concerns are a priority for many patients. If there is a risk of noticeable scarring or damage, a patient may wish to ask about alternative types of removal or inquire about the services of a plastic surgeon.

QUESTIONS TO ASK THE DOCTOR

- What treatment(s) would you recommend for my tumor?
- How effective would you expect each of them to be, for a tumor of this size and in this location?
- How much cosmetic damage am I likely to see with each?
- Are there any alternatives?
- How should I prepare for the procedure?
- What is the risk that my tumor in particular will grow again?

After treatment, it is important to return to the doctor periodically to check for regrowth or new skin cancers. Approximately a third to a half of all patients with non-melanoma skin cancers find a new skin cancer within the next five years. Having a squamous cell carcinoma before the age of 60 may also increase the chance of developing other cancers in internal organs; however, this idea is still very controversial.

See also Basal cell carcinoma; Chemoprevention; Reconstructive surgery.

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Staging *see* **Tumor staging**

Stem cell transplant *see* **Bone marrow transplantation**

Stenting

Definition

Stenting is a procedure in which a cylindrical structure (stent) is placed into a hollow tubular organ to provide artificial support and maintain the patency of the opening. Although it is most often used for cardiovascular functioning, it is also utilized to manage obstructions in cancer patients.

Purpose

Stents are used in cancer patients to relieve obstructions due to:

- direct blockages within the tube (or lumen) due to cancer growth
- narrowing of the lumen from tumor growth outside pressing on the tube and narrowing the lumen
- occasionally from the build up of scar tissue (fibrosis) from radiation therapy

Tumors most likely to cause obstruction requiring stent placement include **esophageal cancer**, bronchogenic **carcinoma**, pancreatic cancer, cancers of the bile duct, and occasionally colorectal carcinomas.

Precautions

Every patient should be viewed individually with special consideration given to the patient's present status. Generally, surgical procedures are for the correction of a problem; but in many cancer cases, relief of symptoms is the only therapeutic option. Since it is extremely difficult to remove or reposition these stents after they are placed, the degree of relief to be offered by its insertion should be significant. The physician and the patient should discuss all alternatives and come to a mutual decision.

KEY TERMS

Endoscope—An instrument used for direct visual inspection of hollow organs or body cavities.

Esophagus—The muscular, membranous structure that extends from the throat to the stomach.

Lumen—The cavity or channel within a tube or tubular organ, such as a blood vessel or the intestine.

QUESTIONS TO ASK THE DOCTOR

- Am I a good candidate for this procedure?
- Do I have any contraindications that should be considered before having the procedure?
- Will I experience any improvement in my quality of life?
- What are the advantages and disadvantages of the procedure?
- Does the physician performing the procedure do this often or only occasionally?

Description

Endoscopic retrograde cholangiopancreatography (ERCP) is the name of the procedure utilized to place most stents for pancreatic and biliary tumors. The ERCP is a flexible endoscope, which can be directed and moved around the many bends in the upper gastrointestinal tract. The newer video endoscopes have a tiny, optically sensitive computer chip at the end which transmits electronic signals up the scope to a computer that displays an image on a large video screen. The scope has an open channel that permits other instruments to be passed through it to perform biopsies, inject solutions, or place stents. Since ERCP uses x-ray films, the procedure takes place in an x-ray area. Initially the throat is anesthetized with a spray solution and the patient is also usually mildly sedated. The endoscope is inserted into the upper esophagus and a thin tube is inserted through it to the main bile duct entering the intestinal area. Dye is injected into the bile duct and/or the pancreatic duct and x-ray films are taken. The patient usually lies on the left side and then turns onto the stomach to allow complete visualization of the ducts. The patient is able to breathe easily throughout the exam and rarely gags. Any gallstones found may be removed or if the duct has become narrowed, an incision can be made using electrocautery (electrical heat) to relieve the blockage. It is also possible to widen narrowed ducts by placing stents in these areas to keep them open. The patient is taken to recovery following the procedure, which takes 20–40 minutes.

Other endoscopes are used to place stents elsewhere in the body. For example, an esophagoscope is used to place stents in cases of esophageal cancer, a bronchoscope is used for procedures involving endobronchial obstructions, and a colonoscope is used in cases of colorectal obstructions.

Preparation

The patient is instructed not to eat or drink anything for eight hours prior to the procedure. Some physicians may request that no asprin be taken for a certain time period prior to the procedure to prevent excessive bleeding.

Aftercare

The patient may go home after the procedure or may spend one or two nights in the hospital. **Antibiotics** may be given especially if there has been long-standing biliary obstruction. Dietary restrictions are common after esophageal and colorectal stenting.

Risks

The most serious risk associated with the placement of a stent is the risk of perforation. If a tear is made, leakage with life-threatening infection may occur. Migration or recurrent obstruction may necessitate repeat stenting if possible. Occasionally bleeding may occur.

Normal results

Relief of the obstruction with resumption of the ability to eat, breathe, normally clear fluids from the liver or pancreas, or allow normal passage of stool is the desired result of this procedure.

Abnormal results

A sudden change in the degree of pain and/or **fever** that persists as well as any unusual changes should be communicated immediately to a physician.

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Stereotactic needle biopsy

Definition

Stereotactic needle **biopsy** (SNB) is an ultrasound-guided and mammogram-directed needle aspiration biopsy of breast tissue. It is a diagnostic procedure used to determine the cause of radiographic abnormalities in breast tissue.

Purpose

Stereotactic needle biopsy is performed when nonpalpable (unable to be felt) abnormalities are identified by mammogram. The abnormality is generally located on a routine screening mammogram. This biopsy procedure uses a large (core) or small (fine) needle that withdraws samples of the abnormal breast tissue. The doctor uses either the mammogram or an ultrasound image of the abnormal tissue to guide the needle to the biopsy site. The needle is used to remove tissue samples of the site for laboratory analysis.

Description

The patient is made comfortable with a local anesthesia injection prior to the start of the procedure. Special imaging techniques are used to localize (easily see) the abnormal spot. First, the patient lies face down on a table with breasts suspended through an opening. Then mammograms are taken of the suspicious site from several different angles. This technique creates a virtual three-dimensional (stereotactic) picture of the abnormal area. A computer is used to guide the needle to the site for sample removal. If the abnormality can be seen easily on ultrasound, the biopsy may be performed with the patient lying on her back while ultrasound imaging localizes the abnormality. The samples are examined in the laboratory by a pathologist (a physician trained in identification of pathological or abnormal findings) to determine if cancer cells are present.

There are two different types of needles used for stereotactic needle biopsy. The procedures are similar, but the size of the needle varies. A fine-needle biopsy is most often used, in conjunction with ultrasound imaging, when a cyst is suspected. The doctor is able to suction a sample of fluid or tissue through the needle and send it for analysis. The needle is smaller and so is the sample of fluid or tissue extracted. In a core needle biopsy, the needle is larger, has a cutting edge, and enables the physician to extract a larger tissue sample from the suspicious area. A larger tissue sample can enhance laboratory accuracy in identifying the presence of cancer cells.

Preparation

Prior to ordering a breast biopsy, the physician gathers as much information from the patient as possible by asking questions that provide a medical history. The physician will perform a clinical breast examination through palpation to determine any changes from previous exams or to determine a baseline exam. The physician orders a routine screening mammogram (**x ray**) and interprets the results. If something abnormal is revealed on mammogram, further radiologic exams are requested. After confirming the presence of a radiographic abnormality, the physician will order a biopsy. A patient's written informed consent is necessary before any invasive procedure. The document should explain, in understandable language, the patient's treatment options, risks and benefits of the procedure, and potential complications.

General anesthesia is not used for the stereotactic needle biopsy procedure. Usually the physician will use a local injectable anesthetic agent at the needle insertion site to numb the area. When the anesthetic is injected at the biopsy site, the patient will feel a stinging sensation. The physician will wait until the numbing agent takes effect, then proceed with the biopsy. At this point, the patient should only feel a pressure sensation as the needle is guided to the biopsy site.

Precautions

Patients should discuss the indications (reasons for) and contraindications (reasons why not) of having a stereotactic needle biopsy performed with their doctor. While the procedure has been studied extensively with positive outcomes for accuracy of results, it is most indicated in cases where there is a non-palpable area of abnormal tissue identified by mammogram. However, vaguely palpable abnormalities can also be managed in this way. Physicians divide "abnormal findings" into several categories. A probable benign finding is a category 3, a suspicious abnormal finding is a category 4, and a highly suggestive of malignancy finding is a category 5.

When there is a probable benign finding (category 3), frequently there is no previous mammogram for comparison study. A stereotactic needle biopsy is done on a category 3 finding when there is a strong family history of **breast cancer**. Usually, a category 3 finding requires only a six month follow-up with **mammography**.

When there is a suspicious abnormality (category 4), a sterotactic needle biopsy is most useful, as well as indicated. In this category, stereotactic needle biopsy is used to differentiate those patients requiring surgical intervention from those needing clinical and mammographic (x-ray) follow-up.

In a category 5 finding, highly suggestive of malignancy, the physician can use information from a stereotactic needle biopsy to confirm a diagnosis and expedite surgical intervention in this category.

Stereotactic needle biopsy is not indicated in all cases where there is nonpalpable breast tissue abnormality. The size of the patient and size of the breast must be considered because a certain breast thickness is necessary for mammogram-guided biopsy. There is no such requirement for ultrasound-guided procedures. Abnormalities just under the skin are technically difficult for the placement of the biopsy needle and are best excised (removed) in an open surgical procedure. Also, areas of breast tissue micro-calcification (tiny areas of thickened breast tissue) that are not closely clustered together can be difficult to visualize in a stereotactic system and therefore difficult to retrieve during biopsy. Finally, the patient must be able to remain still and lie face down for the duration of the biopsy procedure (20 to 40 minutes). Any movement by the patient can render the localization of the abnormal site invalid.

Aftercare

After the procedure, the patient may experience pain or discomfort at the biopsy site. Mild bruising can also occur at the site. For these reasons, the physician may suggest that activities be limited for 24 to 48 hours post-procedure. The physician will suggest or prescribe a medication for discomfort relief. Often, a sport bra or other firm support garment will minimize breast movement and increase post-procedure comfort. Icing the area may also be reccommended. The physician will inform the patient of further follow-up care needed to monitor the patient's ongoing breast health and the subsequent intervals for follow-up imaging.

Risks

It is very important for the patient who is facing a stereotactic needle biopsy procedure to know that there is the possibility of needing a repeat biopsy procedure. A repeat biopsy is necessary if there is a discrepancy between the radiology reports and the pathologist's findings from laboratory analysis of the sample (concordance). As with any procedure, there is a slight risk of allergic reaction to anesthesia. To be well informed, patients should consult with their physician about the risks prior to undergoing SNB.

QUESTIONS TO ASK THE DOCTOR

- What type of physician performs a stereotactic needle biopsy?
- How long will it take to interpret the biopsy results?
- What type of pain management will be used during the procedure?
- Can the biopsy give false negative results?
- Will I have a fine needle biopsy or core biopsy? Why?

Results

Stereotactic needle biopsy is a diagnostic tool used to determine the presence of cancer cells. It is not a therapy used to obliterate an area of abnormal tissue. The results of the biopsy help the physician to determine the best medical or surgical options available to the patient. The biopsy results are reviewed by the physician performing the SNB and by the pathologist who analizes the sample. Results are reviewed and discussed with the patient and options for further treatment or follow up are presented. The patient, with the guidance and expertise of the physician, selects a course of therapy.

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Stereotactic surgery

Definition

Stereotactic surgery is an approach to cancer diagnosis and treatment that makes use of a system of three-dimensional coordinates to locate a site (most commonly within the brain) as precisely as possible for **biopsy** or surgery. The English word *stereotactic* is a combination of a Greek root, *stereo-*, which means "solid" or "having three dimensions," and the Latin word *tactus*, which means "touch." Stereotactic neurosurgery may make use of a conventional incision and drill to enter the patient's skull or precisely focused beams of radiation to destroy cancerous tissue. This second method, which is called stereotactic radiosurgery, is not surgery in the usual sense of the word because no incision is involved.

Purpose

Stereotactic surgery may be performed either to obtain a tissue sample for biopsy or to remove or destroy the tumor itself. As of the early 2000s, stereotactic biopsies are the preferred method of confirming a diagnosis of a brain tumor, because of their precision and because they may offer the only method of obtaining a tissue sample if the tumor is located deep within the brain or close to structures that control vital functions. Stereotactic surgery may also be used in the diagnosis of epilepsy; since the areas of abnormal brain activity in epilepsy cannot always be identified by **imaging studies**, a neurosurgeon can use a stereotactic system to place electrodes for recording brain waves in the areas suspected of being the focus of seizures.

Stereotactic surgery can be used to treat movement disorders as well as brain tumors. In fact, the first clinical application of stereotactic systems in human medicine was in the treatment of schizophrenia in the late 1940s, followed by the use of stereotactic surgery to treat Parkinson's disease and chronic pain in the 1950s. As of the early 2000s, stereotactic surgery is used to treat such other movement disorders as Huntington's chorea and essential tremor, and to insert catheters into the brain to drain abnormal collections of fluid resulting from head injuries, hydrocephalus, or cysts.

Stereotactic radiosurgery can be used to treat movement disorders, malformations of blood vessels, and benign tumors (acoustic neuromas, pituitary adenomas, and meningiomas) as well as malignant tumors of the brain and spinal cord. It may also be used to treat cancers in the nose or other small and well-defined parts of the body, or as a follow-up "booster" treatment for patients with recurrent tumors who have already received the maximum safe dose of conventional **radiation therapy**.

Precautions

Stereotactic surgery or radiosurgery should be done only by qualified specialists who are experienced in these techniques, and performed only in treatment centers with the necessary high-level equipment.

Stereotactic radiosurgery with a gamma knife is most effective in treating relatively small tumors (an inch or less in diameter) with well-defined borders that have not invaded the brain; in addition, it is usually reserved for patients with a life expectancy of six months or longer. Large brain tumors may require partial removal by conventional open surgery prior to treatment with radiosurgery.

Description

Stereotactic surgery

The earliest forms of stereotactic surgery in humans developed out of an apparatus that was designed by Victor Horsley and Henry Clarke in 1906 to study brain functions in monkeys. It was not until 1946, however, that two American researchers designed a stereotactic frame to guide brain surgery in humans. There were two difficulties in transferring a stereotactic system from other mammals to humans, however; one problem was the much greater degree of variation among humans in the location of various bony landmarks on the skull that were used to identify the approximate location of various parts of the brain. The other problem was the lack of a reliable imaging method for visualizing internal brain structures.

By the 1940s, a method known as positive contrast ventriculography, in which some of the cerebral fluid in the ventricles of the brain was withdrawn and replaced with air or another contrast medium that would show up on an x-ray, allowed surgeons to identify structures within the brain in relation to one another. Ventriculography made it possible to use such internal structures as the posterior commissure or pineal gland rather than various points on the outside of the skull as landmarks for brain surgery. Researchers compiled stereotactic atlases, or collections of photographs of cross-sections of brain tissue, with reference grids around the borders of each photograph. A surgeon could consult one of these atlases in order to calculate the exact location of a targeted brain

structure with reference to the posterior commissure. Present-day stereotactic surgery still makes use of atlases, although they are now compiled from computer images rather than photographs.

The first frame that was used in stereotactic surgery in the 1940s consisted of a plaster cap fitted to the individual patient with a head ring and electrode carrier mounted to it. In the early 2000s, however, stereotactic surgery makes use of a base ring attached to the patient's skull, a CT or MRI scan, and an arc ring to guide the surgeon in drilling a hole through the skull. After the base ring is attached to the patient's scalp, he or she is taken to the operating room, where the base ring is attached to the operating table in order to hold the patient's head steady. The entry site for the surgeon's drill is selected, and the entry site and area of the tumor are located on a phantom image that relates these points to the patient's head. Coordinates derived from the phantom image are entered into a computer that determines the final path of the surgeon's instruments. An arc ring is then attached to the base ring to guide the surgeon's movements. This stereotactic s! ystem allows the surgeon to make only a very small incision (less than in long) in the scalp, and drill a hole smaller in diameter than a pencil in order to insert a biopsy needle or electrode.

Some medical centers use a frameless method for stereotactic brain surgery. In this method, images of the patient's head from CT or MRI scans are uploaded into a computer for display on a monitor. Markers on the patient's skin are registered by a probe linked to the computer by a camera, which joins the position of the patient's head on the operating table to the images on the computer monitor. In addition, the surgeon's instruments contain light-emitting diodes (LEDs) that are tracked by the computer during the operation.

Stereotactic radiosurgery and radiotherapy

Stereotactic radiosurgery (SRS) can be performed with three different types of machines to provide the radiation used to kill the tumor cells. The gamma knife is a stationary unit that contains 201 sources of gamma rays derived from cobalt-60 that can be focused by a computer on a single small area of the brain. The radiation can be directed very precisely to the tumor without destroying nearby healthy tissue. The patient lies on a couch with a large helmet attached to his or her headframe. The helmet contains holes that allow beams of radiation to enter. The couch is then slid into a gantry containing the cobalt-60. Treatment time varies from several minutes to over an hour, depending on the size, shape, and location of the tumor. Gamma knife radiosurgery is usually a single-dose treatment.

Radiosurgery can also be performed with a linear accelerator (also called a LINAC), which is a device that produces high-energy photons that can be used to treat larger tumors, metastatic tumors, or arteriovenous malformations. Linear accelerators are preferred for multisession treatments using smaller doses of radiation. Radiosurgery performed with divided doses is known as fractionated radiosurgery; some doctors prefer to call it fractionated stereotactic radiotherapy, or FSR. The advantage of fractionated treatment is that it allows a higher total dose of radiation to be delivered to the tumor without harming nearby normal tissues. The beams of radiation from a LINAC are shaped to a very high degree of accuracy by metal tubes known as collimators. Unlike the gamma knife unit, the LINAC moves around the patient during treatment, delivering arcs of radiation matched by computer to the shape of the tumor.

The third type of machine that can be used for radiosurgery is a cyclotron, which is a nuclear reactor used to accelerate charged particles (usually protons or ions) to high levels of energy that can be used for radiosurgery. Cyclotrons are available in very few locations as of 2005, however, and there have been few **clinical trials** comparing radiosurgery performed with a cyclotron to radiosurgery using a gamma knife or LINAC.

Preparation

Some cancer centers use an invasive form of preparation for stereotactic surgery or radiosurgery. In this method, the patient is not allowed food or drink after midnight the night before the procedure. He or she is given an intravenous sedative in the morning; local anesthetic is then applied at four points on the scalp. It is not necessary to shave the head. After the skin has been numbed, the surgeon fastens the base ring to the patient's skull with four pins, the insertion points of the pins determined by the location of the brain tumor. The patient is then given a CT or MRI scan. The resultant image allows the surgeon to calculate the exact area of the tumor in three dimensions. The planning and procedure may take anywhere from three to 12 hours.

Other cancer centers use a less invasive form of patient preparation that consists of an individualized mouthpiece used to attach a headframe (or ''halo'' to the patient's head. The headframe is used to prevent the head from moving during treatment as well as to position the head precisely.

Stereotactic radiosurgery is always preceded by a careful review of the patient's records to make sure that this type of treatment is appropriate for the tumor. The patient may be given steroid medications to control swelling of brain tissue or antiepileptic drugs to prevent seizures prior to radiosurgery.

If the patient is to receive fractionated radiosurgery or FSR, he or she will be given a simulation scan prior to treatment. The simulation scan allows the neurosurgeon to plan the treatment by making a set of images that show the exact location of the tumor in relation to normal brain tissue. The first step is the creation of a thermoplastic mask that will allow the doctor to position the patient's head precisely each time the patient receives a treatment. Next, the patient is positioned in a scanner while wearing the mask. The simulation scan takes about two and a half hours. When the patient returns for a treatment session about a week later, the molded thermoplastic mask is used to reposition the patient's head in the exact location that was used for the simulation scan. Fractionated treatments usually take between 30 and 90 minutes to complete.

A preparatory scan is not needed with some newer lightweight linear accelerators, which make use of a robot to position the dose of radiation rather than a frame to hold the patient's head in place. If the patient moves during treatment, the robot detects the movement and repositions the linear accelerator before delivering the radiation beam.

Aftercare

Stereotactic surgery

After the surgeon has completed the procedure, he or she closes the scalp incision—usually with only one stitch—and removes the base ring from its attachment points on the scalp by unscrewing the pins. These holes are small and do not require stitches, although an antibiotic medication is applied to prevent infection. The patient is taken to a recovery room, remains in the hospital overnight for observation, and goes home the next day. Patients must arrange for a friend or relative to drive them home. A follow-up visit with the neurosurgeon is scheduled for six to 12 weeks after treatment.

Stereotactic radiosurgery and radiotherapy

Patients receiving gamma knife treatment can be treated as outpatients, returning home after the procedure. If pins were used to attach a headframe to the patient's scalp, the head will be wrapped with gauze for about two hours before the patient is discharged.

Risks

Stereotactic surgery

The risks of stereotactic surgery are similar to those of other surgical procedures involving open incisions in the head or neck:

- infection
- scarring
- pain
- incomplete removal of the tumor
- swelling of brain tissue
- worsening of neurologic symptoms
- anesthesia reaction

KEY TERMS

Atlas—In anatomy, a collection of medical illustrations of one specific subject, such as the brain or heart. Detailed atlases of the brain are important guides for surgeons performing stereotactic neurosurgery.

Collimator—A metal tube designed to control the size and direction of a beam of radiation.

Cyclotron—A machine that accelerates charged atomic particles within a constant magnetic field.

Fractionated—In radiotherapy, treatment that is divided into several sessions of smaller doses of radiation rather than one large dose delivered in a single session.

Gamma knife—The name for a specific type of radiosurgery that uses highly focused cobalt-60 radiation to destroy cancerous tissue in the brain. It is not a knife in the conventional sense.

Hydrocephalus—A condition marked by the buildup of cerebrospinal fluid within the skull, causing increased pressure on the brain and a variety of neurologic symptoms. Stereotactic surgery may be used to place a catheter within the brain in order to drain the excess fluid.

Landmark—An anatomical structure that is easy to recognize and suitable as a reference point in locating other structures or making measurements.

Photon—A quantum of electromagnetic radiation with no mass and no charge.

Posterior commissure—A bundle of fibers that connects the two cerebral hemispheres near the third ventricle of the brain.

Radiosurgery—A form of cancer treatment in which tissue is destroyed by radiation from an external source or an implant rather than by manual removal. In spite of its name, radiosurgery is not surgery in the usual sense of making an incision, removing tissue, and then closing the incision.

Ventricles—Small cavities within the brain filled with cerebrospinal fluid.

QUESTIONS TO ASK YOUR DOCTOR

- Is stereotactic radiosurgery an option for treatment of my tumor?
- How much experience have you had with this form of treatment?
- What do you consider the advantages and drawbacks of gamma knife and linear accelerator radiosurgery?
- What are the risks of this treatment in my particular case?

Stereotactic radiosurgery

The risks of stereotactic radiosurgery are similar to those for other forms of radiation treatment of the brain or spinal cord:

- nausea and vomiting
- headaches
- dizziness
- fatigue
- hair loss
- radiation necrosis (a group or collection of dead brain cells)
- leukoencephalopathy (damage to the white matter of the brain)
- swelling of brain tissue

Normal results

Normal results of stereotactic surgery include the obtaining of an appropriate tissue sample for biopsy or the removal of cancerous tissue. Normal results of stereotactic radiosurgery include the shrinkage or death of cancer cells in the brain or spinal cord, the drainage of excess cerebrospinal fluid, or improvement in tremor and other symptoms of Parkinson's disease or Huntington's chorea.

Abnormal results

Abnormal results for stereotactic radiosurgery would include the failure of the tumor to respond to treatment.

See also Brain tumors; Radiation therapy.

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Rebecca Frey, PhD

STI-571 *see* **Imatinib mesylate**

Stomach cancer

Definition

Stomach cancer (also known as gastric cancer) is a disease in which the cells forming the inner lining of the stomach become abnormal and start to divide uncontrollably, forming a mass called a tumor.

Description

The stomach is a J-shaped organ that lies in the left and central portion of the abdomen. The stomach produces many digestive juices and acids that mix with the

food and aid in the process of digestion. There are five regions of the stomach that doctors refer to when determining the origin of stomach cancer. These are:

- the cardia, area surrounding the cardiac sphincter which controls movement of food from the esophagus into the stomach;
- the fundus, upper expanded area adjacent to the cardiac region;
- the antrum, lower region of the stomach where it begins to narrow;
- the prepyloric, region just before or nearest the pylorus;
- and the pylorus, the terminal region where the stomach joins the small intestine. Cancer can develop in any of the five sections of the stomach. Symptoms and outcomes of the disease will vary depending on the location of the cancer.

Demographics

Based on previous data from the National Cancer Institute and the United States Census, the American Cancer Society estimates that 21,700 Americans will be diagnosed with stomach cancer during 2001 and approximately 13,000 deaths will result from the disease. In most areas, men are affected by stomach cancer nearly twice as often as women. Most cases of stomach cancer are diagnosed between the ages of 50 and 70 but in families with a hereditary risk of stomach cancer, younger cases are more frequently seen.

Stomach cancer is one of the leading causes of cancer deaths in several areas of the world, most notably Japan and other Asian countries. In Japan it appears almost ten times as frequently as in the United States. The number of new stomach cancer cases is decreasing in some areas, however, especially in developed countries. In the United States, incidence rates have dropped from 30 individuals per 100,000 in the 1930s, to only 8 in 100,000 individuals developing stomach cancer by the 1980s. The use of refrigerated foods and increased consumption of fresh fruits and vegetables, instead of preserved foods with high salt content, may be a reason for the decline.

Causes and symptoms

While the exact cause for stomach cancer has not been identified, several potential factors have lead to increased numbers of individuals developing the disease and therefore, significant risk has been associated. Diet, work environment, exposure to the bacterium *Helicobacter pylori*, and a history of stomach disorders such as ulcers or polyps are some of these believed causes.

Studies have shown that eating foods with high quantities of salt and nitrites increases the risk of stomach cancer. The diet in a specific region can have a great impact on its residents. Making changes to the types of foods consumed has been shown to decrease likelihood of disease, even for individuals from countries with higher risk. For example, Japanese people who move to the United States or Europe and change the types of foods they eat have a far lower chance of developing the disease than do Japanese people who remain in Japan and do not change their dietary habits. Eating recommended amounts of fruit and vegetables may lower a person's chances of developing this cancer.

A high risk for developing stomach cancers has been linked to certain industries as well. The best proven association is between stomach cancer and persons who work in coal mining and those who work processing timber, nickel, and rubber. An unusually large number of these workers have been diagnosed with this form of cancer.

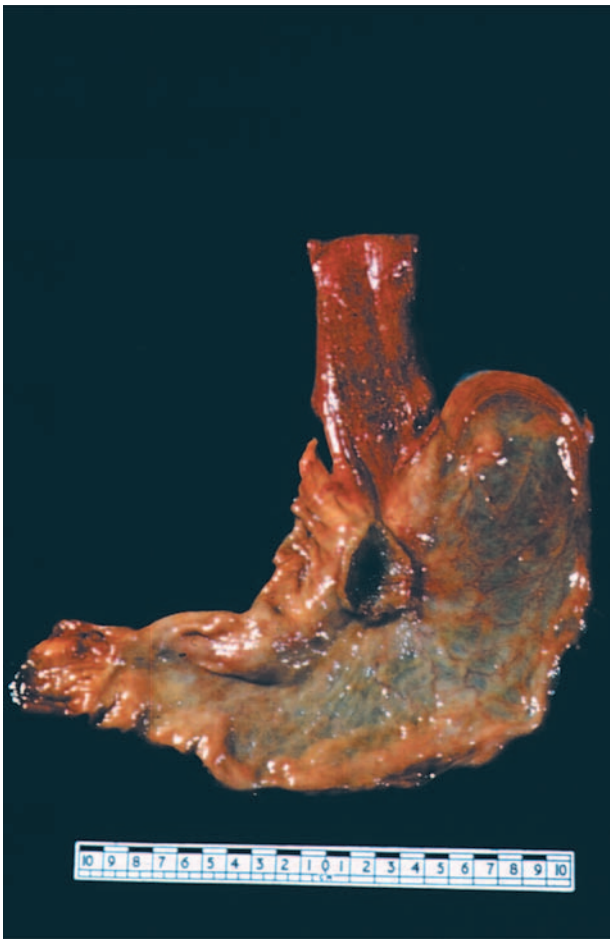
Several studies have identified a bacterium (*Helicobacter pylori*) that causes stomach ulcers (inflammation in the inner lining of the stomach). Chronic (long-term) infection of the stomach with these bacteria may lead to a particular type of cancer (lymphomas or mucosa-associated lymphoid tissue [MALT]) in the stomach.

Another risk factor is the development of polyps, benign growths in the lining of the stomach. Although polyps are not cancerous, some may have the potential to turn cancerous. People in blood group A are also at elevated risk for this cancer for unknown reasons. Other speculative causes of stomach cancer include previous stomach surgery for ulcers or other conditions, or a form of **anemia** known as pernicious anemia.

Stomach cancer is a slow-growing cancer. It may be years before the tumor grows very large and produces distinct symptoms. In the early stages of the disease, the patient may only have mild discomfort, indigestion, heartburn, a bloated feeling after eating, and mild nausea. In the advanced stages, a patient will have loss of appetite and resultant **weight loss**, stomach pains, vomiting, difficulty in swallowing, and blood in the stool. Stomach cancer often spreads (metastasizes) to adjoining organs such as the esophagus, adjacent lymph nodes, liver, or colon.

Diagnosis

Unfortunately, many patients diagnosed with stomach cancer experience pain for two or three years before informing a doctor of their symptoms. When a doctor suspects stomach cancer from the symptoms described



An excised section of a human stomach showing a cancerous tumor (center, triangular shape). *(Custom Medical Stock Photo. Reproduced by permission.)*

by the patient, a complete medical history will be taken to check for any risk factors. A thorough physical examination will be conducted to assess all the symptoms. Laboratory tests may be ordered to check for blood in the stool (**fecal occult blood test**) and anemia (low red blood cell count), which often accompany gastric cancer.

In some countries, such as Japan, it is appropriate for patients to be given routine screening examinations for stomach cancer, as the risk of developing cancer in that society is very high. Such screening might be useful for all high-risk populations. Due to the low prevalence of stomach cancer in the United States, routine screening is usually not recommended unless a family history of the disease exists.

Whether as a **screening test** or because a doctor suspects a patient may have symptoms of stomach cancer, endoscopy or barium x rays are used in diagnosing stomach cancer. For a barium **x ray** of the upper gastrointestinal tract, the patient is given a chalky, white solution of barium sulfate to drink. This solution coats the esophagus, the stomach, and the small intestine. Air may be pumped into the stomach after the barium solution in order to get a clearer picture. Multiple x rays are then taken. The barium coating helps to identify any abnormalities in the lining of the stomach.

In another more frequently used test, known as **upper gastrointestinal endoscopy**, a thin, flexible, lighted tube (endoscope) is passed down the patient's throat and into the stomach. The doctor can view the lining of the esophagus and the stomach through the tube. Sometimes, a small ultrasound probe is attached at the end of the endoscope. This probe sends high frequency sound waves that bounce off the stomach wall. A computer creates an image of the stomach wall by translating the pattern of echoes generated by the reflected sound waves. This procedure is known as an endoscopic ultrasound or EUS.

Endoscopy has several advantages, in that the physician is able to see any abnormalities directly. In addition, if any suspicious-looking patches are seen, **biopsy** forceps can be passed painlessly through the tube to collect some tissue for microscopic examination. This is known as a biopsy. EUS is beneficial because it can provide valuable information on depth of tumor invasion.

After stomach cancer has been diagnosed and before treatment starts, another type of x-ray scan is taken. **Computed tomography** (CT) is an imaging procedure that produces a three-dimensional picture of organs or structures inside the body. CT scans are used to obtain additional information in regard to how large the tumor is and what parts of the stomach it borders; whether the cancer has spread to the lymph nodes; and whether it has spread to distant parts of the body (metastasized), such as the liver, lung, or bone. A CT scan of the chest, abdomen, and pelvis is taken. If the tumor has gone through the wall of the stomach and extends to the liver, pancreas, or spleen, the CT will often show this. Although a CT scan is an effective way of evaluating whether cancer has spread to some of the lymph nodes, it is less effective than EUS in evaluating whether the nodes closest to the stomach are free of cancer. However, CT scans, like barium x-rays, have the advantage of being less invasive than upper endoscopy.

Laparoscopy is another procedure used to stage some patients with stomach cancer. This involves a medical device similar to an endoscope. A laparoscopy is a minimally invasive surgery technique with one or a few small incisions, which can be performed on an outpatient basis, followed by rapid recovery. Patients who may receive **radiation therapy** or **chemotherapy** before surgery may undergo a laparoscopic procedure to determine the precise stage of cancer. The patient with **bone pain**

or with certain laboratory results should be given a bone scan.

Benign gastric neoplasms are tumors of the stomach that cause no major harm. One of the most common is called a submucosal leiomyoma. If a leiomyoma starts to bleed, surgery should be performed to remove it. However, many leiomyomas require no treatment. Diagnosis of stomach cancers should be conducted carefully so that if the tumor does not require treatment the patient is not subjected to a surgical operation.

Clinical staging and prognosis

More than 95% of stomach cancers are caused by adenocarcinomas, malignant cancers that originate in glandular tissues. The remaining 5% of stomach cancers include lymphomas and other types of cancers. It is important that gastric lymphomas be accurately diagnosed because these cancers have a much better prognosis than stomach adenocarcinomas. Approximately half of the people with gastric lymphomas survive five years after diagnosis. Treatment for gastric **lymphoma** involves surgery combined with chemotherapy and radiation therapy.

Staging of stomach cancer is based on how deep the growth has penetrated the stomach lining; to what extent (if any) it has invaded surrounding lymph nodes; and to what extent (if any) it has spread to distant parts of the body (metastasized). The more confined the cancer, the better the chance for a cure.

One important factor in the staging of adenocarcinoma of the stomach is whether or not the tumor has invaded the surrounding tissue and, if it has, how deep it has penetrated. If invasion is limited, prognosis is favorable. Diseased tissue that is more localized improves the outcome of surgical procedures performed to remove the diseased area of the stomach. This is called a resection of the stomach.

Several distinct ways of classifying stomach cancer according to cell type have been proposed. The Lauren classification is encountered most frequently. According to this classification system, gastric adenocarcinomas are either called intestinal or diffuse. Intestinal cancers are much like a type of intestinal cancer called intestinal **carcinoma**. Intestinal tumors are more frequently found in males and in older patients. The prognosis for these tumors is better than that for diffuse tumors. Diffuse tumors are more likely to infiltrate, that is, to move into another organ of the body.

Treatment

Because symptoms of stomach cancer are so mild, treatment often does not commence until the disease is well advanced. The three standard modes of treatment for stomach cancer include surgery, radiation therapy, and chemotherapy. While deciding on the patient's treatment plan, the doctor takes into account many factors. The location of the cancer and its stage are important considerations. In addition, the patient's age, general health status, and personal preferences are also taken into account.

Surgery

In the early stages of stomach cancer, surgery may be used to remove the cancer. Surgical removal of adenocarcinoma is the only treatment capable of eliminating the disease. Laparoscopy is often used before surgery to investigate whether or not the tumor can be removed surgically. If the cancer is widespread and cannot be removed with surgery, an attempt will be made to remove blockage and control symptoms such as pain or bleeding. Depending on the location of the cancer, a portion of the stomach may be removed, a procedure called a partial gastrectomy. In a surgical procedure known as total gastrectomy, the entire stomach may be removed. However, doctors prefer to leave at least part of the stomach if possible. Patients who have been given a partial gastrectomy achieve a better quality of life than those having a total gastrectomy and typically lead normal lives. Even when the entire stomach is removed, the patients quickly adjust to a different eating schedule. This involves eating small quantities of food more frequently. High protein foods are generally recommended.

Partial or total gastrectomy is often accompanied by other surgical procedures. Lymph nodes are frequently removed and nearby organs, or parts of these organs, may be removed if cancer has spread to them. Such organs may include the pancreas, colon, or spleen.

Preliminary studies suggest that patients who have tumors that cannot be removed by surgery at the start of therapy may become candidates for surgery later. Combinations of chemotherapy and radiation therapy are sometimes able to reduce disease for which surgery is not initially appropriate. Preliminary studies are being performed to determine if some of these patients can become candidates for surgical procedures after such therapies are applied.

Chemotherapy

Whether or not patients undergoing surgery for stomach cancer should receive chemotherapy is a controversial issue. Chemotherapy involves administering anticancer drugs either intravenously (through a vein in the arm) or orally (in the form of pills). This can either be used as the primary mode of treatment or after surgery to destroy any cancerous cells that may have migrated to distant sites. Most cancers of the gastrointestinal tract do

not respond well to chemotherapy, however, adenocarcinoma of the stomach and advanced stages of cancer are exceptions.

Chemotherapy medicines such as **doxorubicin**, mitomycin C, and 5-fluorouracil (5-FU or fluorouracil), used alone, provide benefit to at least one in five patients. Combinations of agents may provide even more benefit, although it is not certain that this includes longer survival. For example, some doctors use what is called the FAM regimen, which combines 5-fluorouacil, doxorubicin, and mitomycin. Some doctors prefer using 5-fluorouracil alone to FAM since side effects are more moderate. Another combination some doctors are using involve high doses of the medications **methotrexate**, 5- **fluorouracil**, and doxorubicin. Other combinations that have shown benefit include the ELF regimen, a combination of **leucovorin**, 5- fluorouracil, and **etoposide**. The EAP regimen, a combination of etoposide, doxorubicin, and **cisplatin** is also used.

Although chemotherapy using a single medicine is sometimes used, the best response rates are often achieved with combinations of medicines. Therefore, in addition to studies exploring the effectiveness of new medicines there are other studies attempting to evaluate how to best combine existing forms of chemotherapy to bring the greatest degree of help to patients.

Radiation therapy

Radiation therapy is often used after surgery to destroy the cancer cells that may not have been completely removed during surgery. To treat stomach cancer, external beam radiation therapy is generally used. In this procedure, high-energy rays from a machine that is outside of the body are concentrated on the area of the tumor. In the advanced stages of stomach cancer, radiation therapy is used to ease the symptoms such as pain and bleeding. However, studies of radiation treatment for stomach cancer have shown that the way it has been used it has been ineffective for many patients.

Researchers are actively assessing the role of chemotherapy and radiation therapy used before a surgical procedure is conducted. They are searching for ways to use both chemotherapy and radiation therapy so that they increase the length of survival of patients more effectively than current methods are able to do.

Prognosis

Overall, approximately 20% of patients with stomach cancer live at least five years following diagnosis. Patients diagnosed with stomach cancer in its early stages have a far better prognosis than those for whom it is in the later stages. In the early stages, the tumor is small, lymph nodes are unaffected, and the cancer has not migrated to the lungs or the liver. Unfortunately,

KEY TERMS

Adenocarcinoma—Malignant cancers that originate in the tissues of glands or that form glandular structures.

Anemia—A condition in which iron levels in the blood are low.

Barium x ray (upper GI)—An x-ray test of the upper part of the gastrointestinal (GI) tract (including the esophagus, stomach, and a small portion of the small intestine) after the patient is given a white, chalky barium sulfate solution to drink. This substance coats the upper GI and the x rays reveal any abnormality in the lining of the stomach and the upper GI.

Biopsy—Removal of a tissue sample for examination under the microscope to check for cancer cells.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

Endoscopic ultrasound (EUS)—A medical procedure in which sound waves are sent to the stomach wall by an ultrasound probe attached to the end of an endoscope. The pattern of echoes generated by the reflected sound waves are translated into an image of the stomach wall by a computer.

External radiation therapy—Radiation therapy that focuses high-energy rays from a machine on the area of the tumor.

Infiltrate—A tumor that moves into another organ of the body.

Polyp—An abnormal growth that develops on the inside of a hollow organ such as the colon, stomach, or nose.

Radiation therapy—Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Total gastrectomy—Surgical removal (excision) of the entire stomach.

Upper endoscopy—A medical procedure in which a thin, lighted, flexible tube (endoscope) is inserted down the patient's throat. Through this tube the doctor can view the lining of the esophagus, stomach, and the upper part of the small intestine.

only about 20% of patients with stomach cancer are diagnosed before the cancer had spread to the lymph nodes or formed a distant **metastasis**.

It is important to remember that statistics on prognosis may be misleading. Newer therapies are being developed rapidly and five-year survival has not yet been measured with these. Also, the largest group of people diagnosed with stomach cancer are between 60 and 70 years of age, suggesting that some of these patients die not from cancer but from other age-related diseases. As a result, some patients with stomach cancer may be expected to have longer survival than did patients just ten years ago.

Coping with cancer treatment

Many patients experience feelings of **depression**, anxiety, and **fatigue** when dealing with the knowledge and treatments associated with stomach cancer. Side effects such as **nausea and vomiting** may also present during treatment. Understanding what to expect as a result of the various treatments and learning about alternative methods for reducing these symptoms may improve the effectiveness of treatments and provide a more positive outlook in regard to the individual's situation. A doctor or other health professional should be consulted to develop strategies for managing any negative symptoms or feelings.

Prevention

Avoiding many of the risk factors associated with stomach cancer may prevent its development. Excessive amounts of salted, smoked, and pickled foods should be avoided, as should foods high in nitrates. A diet that includes recommended amounts of fruits and vegetables is believed to lower the risk of several cancers, including stomach cancer. The American Cancer Society recommends eating at least five servings of fruits and vegetables daily and choosing six servings of food from other plant sources, such as grains, pasta, beans, cereals, and whole grain bread.

Abstaining from tobacco and excessive amounts of alcohol will reduce the risk for many cancers. In countries where stomach cancer is common, such as Japan, early detection is important for successful treatment.

Special concerns

Following gastrectomy or partial gastrectomy it is important for the patient to carefully follow doctor's orders about what foods are eaten and when they should be eaten. In particular, the patient may be asked to have small, frequent meals.

QUESTIONS TO ASK THE DOCTOR

- Has the cancer spread to the lymph nodes?
- Has the cancer spread to the lungs, liver, or spleen?
- (After endoscopy or barium x-rays and CT scan have been completed)Would I benefit from endoscopic ultrasound or laparoscopy?
- (If surgery is recommended) Do recent studies show that it might be a good idea to also use chemotherapy or radiation therapy?
- (If gastrectomy or partial gastrectomy was performed) How should I alter my diet and eating patterns?
- (Following surgery) What foods should I be eating? Is there a registered dietitian I can speak with on a regular basis about what I should eat?

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ORGANIZATIONS

National Coalition for Cancer Survivorship. 1010 Wayne Ave., 7th Floor, Silver Spring, MD 20910-5600. (301) 650-9127 or (877) NCCS-YES. <http://www.cansearch.org>.

Stomach Cancer: Detection and Symptoms. Stomach Cancer: Prevention and Risk Factors. Stomach Cancer: Treatment. Stomach Cancer: What Is It? American Cancer Society. (800) ACS-2345. <http://www.cancer.org>.

What You Need to Know About Stomach Cancer. PDQ Treatment—Patients: Gastric Cancer. The National Cancer Institute. (800) 4-CANCER. <http://www.nci.nih.gov>.

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Bob Kirsch

Stomatitis

Description

Stomatitis describes an inflammation of the mucous membranes of the mouth. This condition, frequently referred to as **mucositis**, can result from cancer treatments such as **chemotherapy** and **radiation therapy**. It is characterized by mouth ulcers or sores, and pain in the mouth. The first symptoms may be sensitivity to spicy foods and reddened mucous membranes. The patient with stomatitis may also experience a dry or swollen tongue, difficulty swallowing, and an inability to eat or drink. It is usually a short-term condition, lasting from just a few days to a few weeks. Reddened areas in the mouth may appear as early as three days after receiving chemotherapy, but normally it is within five to seven days. As time goes on, ulceration occurs. The inflammation can range from mild to severe. If such complications as infection do not occur, stomatitis usually heals completely within two to four weeks.

Although stomatitis is often a short-term problem, it is of concern to cancer patients and health care professionals because it can interfere with the patient's receiving adequate nutrition as well as cause pain and discomfort.

Causes

Stomatitis is most often caused by such cancer treatments as chemotherapy and radiation therapy. Chemotherapy medications work because they are attracted to rapidly growing cells like cancer cells. However, many of the body's normal cells also grow rapidly, and chemotherapy kills them as well. The mouth includes several structures that together are referred to as the oral cavity: the lips, teeth, gums, tongue, pharynx, and the salivary glands. Most of these structures are covered by mucous membranes, the shiny, pink moist lining of the mouth. The outer layer of mucous membranes grows very rapidly, and because of this characteristic they can easily be damaged by chemotherapy and radiation therapy. When these cells are damaged, they slough off, and the lining of the mouth is left vulnerable and without protection. This exposed lining may become inflamed, swollen, and dry, and will often develop ulcers or sores.

Stomatitis caused by radiation therapy normally develops in the area where the radiation is given. It generally begins seven to fourteen days after starting radiation. It will usually exhibit improvement about two to three weeks after the treatment stops.

Stomatitis may also develop as an indirect result of cancer treatment or the cancer itself. Chemotherapy can frequently cause the patient's infection-fighting white blood cells to drop down below normal levels. When this happens, the body may be unable to keep the normal organisms in the oral cavity in balance and stomatitis, as well as such infections as thrush (oral candidiasis), may result. The severity of the stomatitis is dependent on various factors, including the diagnosis, the patient's age, the patient's oral condition before cancer treatment, and the level of oral care during therapy. The duration and severity of the low white blood count is another factor.

Stomatitis may also be caused or worsened by wearing dentures, braces, or other dental appliances that irritate the tissues of the mouth. According to the American Dental Association, about 8.4% of all Americans over the age of 17 have denture stomatitis.

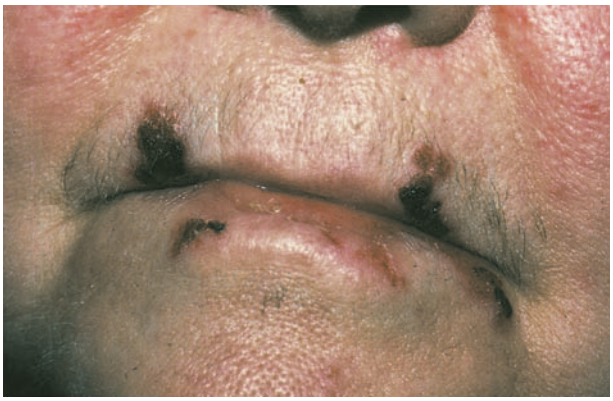
Treatments

Various measures can be taken by the cancer patient to help prevent the occurrence or severity of stomatitis. A carefully followed program of good oral care started before cancer treatment can reduce the severity of stomatitis. The primary preventative measures include good nutritional intake, good oral hygiene practices, and early detection of any oral lesions by either the patient or a health care professional.

Once cancer treatment has started, the patient should carefully observe the mouth daily. The patient should inform their health care professional if any symptoms such as reddened areas, swelling, blisters, sores, white patches, or bleeding are noted. Meticulous oral hygiene and comfort measures are the focus of care. Sometimes, no matter what the patient does, stomatitis occurs. However, if good oral care is performed, the severity of symptoms is usually lessened. The following measures may be recommended to treat stomatitis:

- Rinsing the oral cavity after meals and before bedtime with a mild salt-water or baking soda and water solution will help keep the mouth clean and free of debris.
- A soft-bristled toothbrush or soft foam tooth-cleaning device should be used to keep the mouth and teeth very clean.
- Maintaining a good nutritional intake and drinking adequate amounts of fluids helps the body heal the stomatitis.
- The use of any tobacco products and alcohol should be avoided, as they can irritate the lining of the mouth.
- Avoid spicy or acidic foods, or very hot foods.
- Patients who wear dentures should remove them at night rather than leaving them in the mouth overnight, and should clean them carefully with an antiseptic solution.

Sometimes stomatitis develops in spite of the patient's best efforts. If the mouth sores are painful



A close-up view of patient's mouth with gingivostomatitis cold sores. *(Custom Medical Stock Photo. Reproduced by permission.)*

KEY TERMS

Mucositis—Inflammation of the mucous membranes of the gastrointestinal tract. It is often used interchangeably with stomatitis.

Mucous membranes—The pink, moist, shiny lining of the mouth.

Oral cavity—The collective term for several structures in the mouth: the lips, teeth, gums, tongue, pharynx, and the salivary glands.

Thrush—An infection of the oral mucosa caused by fungi of the genus *Candida*. It is characterized by patches of a whitish curd-like material that can be scraped off, leaving raw and bleeding tissue underneath. Thrush is also known as oral candidiasis.

enough to prohibit eating and drinking, pain medications, including numbing medicines and both non-narcotic and narcotic pain medicines, may be prescribed.

Alternative and complementary therapies

Some preliminary studies have shown glutamine, an amino acid, to be effective in shortening the duration of stomatitis. Topical Vitamin E has also been studied and it shows some suggestions of being an effective therapy in patients with stomatitis. Other small studies suggest that using ice chips or a chamomile mouthwash will decrease the severity of symptoms. However, most of these studies have been small in scope, and cannot definitively claim the effectiveness of the varying treatments. As with anyone undergoing cancer treatment, the patient with stomatitis should consult with their physician or other health care professional regarding the usage of these alternative approaches.

More recently, a group of researchers in Brazil have reported that an extract made from the leaves of *Trichilia glabra*, a plant found in South America, is effective in killing several viruses that cause stomatitis.

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Streptozocin

Definition

Streptozocin is one of the anticancer (antineoplastic) drugs called alkylating agents. It is available in the U.S. under the brand name Zanosar.

Purpose

Streptozocin is primarily used to treat cancer of the pancreas, specifically advanced islet-cell **carcinoma**.

Description

Streptozocin chemically interferes with the synthesis of the genetic material (DNA) of cancer cells, which prevents these cells from being able to reproduce.

Recommended dosage

Streptozocin is given by injection. The dosage prescribed varies widely depending on the patient, the cancer being treated, and whether or not other medications are also being taken.

Precautions

Streptozocin carries a risk of renal (kidney) toxicity. While receiving streptozocin, patients are encouraged to drink extra fluids, since this can increase the amount of urine passed and help prevent kidney problems.

Streptozocin may cause an allergic reaction in some people. Patients with a prior allergic reaction to streptozocin should not take this medication.

Streptozocin also may cause serious birth defects if either the man or the woman is taking this drug at the time of conception or if the woman takes this drug during pregnancy. Streptozocin also may cause miscarriage.

It is not known whether streptozocin is passed from mother to child through breast milk. However, since many drugs are excreted in breast milk and since streptozocin has the potential to adversely affect an infant, breast feeding is not recommended while this medication is being taken.

Streptozocin suppresses the immune system (by damaging white blood cells) and interferes with the normal functioning of certain organs and tissues. For these reasons, it is important that the prescribing physician is aware of any of the following pre-existing medical conditions:

- a current case of, or recent exposure to, chicken pox
- diabetes mellitus
- herpes zoster (shingles)
- a current case, or history of, gout or kidney stones
- all current infections
- kidney disease
- liver disease

Also, because streptozocin damages white blood cells and platelets, patients taking this drug must exercise extreme caution to avoid contracting any new infections or sustaining any injuries that result in bruising or bleeding.

Side effects

The common side effects of streptozocin include:

- fatigue
- loss of appetite (anorexia)
- nausea and vomiting
- increased susceptibility to infection and bleeding
- swelling of the feet or lower legs
- unusual decrease in urination
- temporary hair loss (alopecia)

Diarrhea is a less common side effect that may also occur.

Because streptozocin can damage the kidneys, liver, white blood cells, and platelets, patients taking this medication should be closely monitored for evidence of these adverse side effects. Laboratory tests, including renal function, urinalysis, complete blood count, and liver function, should be done at frequent intervals (approximately weekly) during drug therapy. If evidence of these adverse side effects is found, treatment with streptozocin may be discontinued or the dose may be decreased.

Interactions

Streptozocin should not be taken in combination with any prescription drug, over-the-counter drug, or herbal remedy without prior consultation with a physician. It is particularly important that the prescribing physician be aware of the use of any of the following drugs:

- anti-infection drugs
- carmustine (an anticancer drug)
- cisplatin (an anticancer drug)
- cyclosporine (an immunosuppressive drug)
- deferoxamine (used to remove excess iron from the body)
- gold salts (used for arthritis)
- inflammation or pain medication other than narcotics
- narcotic pain medication containing acetaminophen (Tylenol) or aspirin
- lithium (used to treat bipolar disorder)
- methotrexate (an anticancer drug also used for rheumatoid arthritis and psoriasis)
- penicillamine (used to treat Wilson's disease and rheumatoid arthritis)

KEY TERMS

Antineoplastic—A drug that prevents the growth of a neoplasm by interfering with the maturation or proliferation of the cells of the neoplasm.

Neoplasm—New abnormal growth of tissue.

- phenytoin (an anticonvulsant)
- plicamycin (an anticancer drug)
- tiopronin (used to prevent kidney stones)

See also Pancreatic cancer, endocrine.

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Strontium-89 *see* **Radiopharmaceuticals**

Sun's soup

Definition

A combination of vegetables and herbs, Sun's soup is a complementary therapy and dietary supplement used for its apparent anticancer properties and as a stimulant for the immune system.

Selected Vegetables and *Sun's Soup* are names of various mixtures of vegetables and herbs. These mixtures were developed by Alexander Sun, a Taiwanese biochemist. As of 2005, two formulations of these products are marketed in the United States as dietary supplements.

Purpose

As a complementary therapy, these products are believed to lengthened the survival of patients with advanced **non-small cell lung cancer** or other types of malignant tumors. In general, Sun's soup is used in conjunction with traditional cancer-fighting therapies, such as surgery, radiation, and **chemotherapy**.

Description

Also known as Selected vegetables, Sun's soup was developed by Alexander Sun, a biochemist, in the mid-1980s. Initially, the mixture contained shitake mushroom, mung bean, Hedyotis diffusa, and Scutellaria barbata, all of which are thought to fight cancer and stimulate the immune system. A 1999 study published in *Hepatogastroenterology* by Nakano and colleagues, lentinan, a beta-glucan found in shitake mushrooms, was used as adjunctive therapy with positive results. The authors reported that not only was the survival of the patients with gastric cancer prolonged, but their quality of life was improved. However, the National Cancer Institute asserted that lentinan may not be active when consumed as an ingredient in the soup. But the National Cancer Institute did other substances in shitake mushrooms may offer health benefits.

Sun began to treat other patients with a variant of the original mixture that excluded Hedyotis diffusa and Scutellaria barbata. This second formulation, a freeze-dried powder, was named Selected Vegetables (SV) or Dried Selected Vegetables (DSV). In 1992, Sun began a phase I/II clinical trial to evaluate DSV as a treatment for patients diagnosed with non-small cell lung cancer. By 1999, Sun and colleagues reported their results in an article published in *Nutrition and Cancer*. Knowing that DSV contained anti-tumor components, Sun and colleagues designed their study to measure how well patients tolerated using it on a long-term basis and its influence on the survival of patients with advanced non-small cell lung cancer. Therefore, there were two parts to the study: the toxicity arm and the survival arm. The toxicity arm was comprised of five patients with stage I non-small cell lung cancer, all of whom were asked to add DSV to their daily diet. Sun and colleagues refer to this group as the "toxicity study group (TG)." The survival arm was comprised of 19 patients with stage III or IV non-small cell lung cancer. Six of the 19 patients added DSV to their daily diet; Sun and colleagues referred to these patients as the "treatment group (SVG)." The remaining 13 patients who did not add DSV to their daily diet served as the "control group (CG)."

It is important to note that all the patients were treated with conventional therapies as deemed appropriate for them. TG patients had surgery plus **radiation therapy** or radiation therapy alone. SVG patients had radiation therapy alone or chemotherapy alone. CG patients had radiation therapy alone, chemotherapy alone, surgery plus radiation therapy, or chemotherapy plus radiation therapy with the exception of one patient who received palliative care, which is care that focuses on symptom management and quality of life issues.

With regard to the toxicity arm of the study, Sun and colleagues reported that "no clinical signs of toxicity were found in the TG patients in the 24-month study period." In fact, all five patients had either gained weight or maintained their weight. Another way the researchers measured how well the patients were tolerating the use of DSV was by recording changes in Karnofsky Perform-

ance Status (KPS), which is a common way of assessing a cancer patient's ability to perform routine tasks. A scoring system of 0 to 100 is used with a greater ability to handle everyday tasks associated with higher scores. Four out of the five TG patients had improved scores, which were measured at the time they entered the study and three months later. One TG patient's score remained the same. Two years after diagnosis, all five TG patients had survived and no recurrent tumors were found during follow-up. Furthermore, Sun and colleagues reported that the TG patients used DSV from 17 months to longer than 24 months. This led Sun and his team to conclude that DSV was "safe, nontoxic, and well tolerated."

With regard to the survival arm of the study, Sun and his team stated that "age, KPS, and body mass index of the SVG and CG patients were comparable" when the study began. Almost five months later a second weight measurement was taken that included 9 of the 13 CG patients and all six of the SVG patients. The average **weight loss** for the SVG group was 2.1%, whereas the average weight loss for the CG group was 11.6%. Reported as statistically significant, the group that added DSV to their daily diet clearly retained more body weight than the group that did not. A statistically significant difference was also noted with regard to the KPS scores between the CG group and the SVG group. One to three months after entering the trial, the KPS scores were improved for the SVG group, whereas the scores for the CG group declined. In other words, adding DSV to the daily diet of the patients in the SVG group not only appeared to help them avoid a decline in condition, but it was also associated with an actual improvement in condition. Furthermore, the median survival time of the CG patients was four months, whereas the median survival time of the SVG patients was 15.5 months. This statistically significant difference reported by Sun and his team supports the notion that adding DSV to the daily diet of a stage III or IV non-small cell lung cancer patient helps to prolong his or her life.

Encouraged by these results, Sun and his team reformulated the mixture and embarked on a pilot study to investigate its anticancer components, which was published in 2001 in *Nutrition and Cancer*. This third formulation was referred to as frozen selected vegetables (FSV). Through the use of a lung tumor model, tumor growth was assessed in mice. According to Sun and his team, a daily portion of FSV was "found to contain 63 mg of inositol hexaphosphate [found in legumes], 4.4 mg of daidzein [found in soy products], 2.6 mg of genistein [found in soy products], and 16 mg of coumestrol [estrogen-like substance found in plants]." Sun et al reported that mouse food containing 5% of FSV "was associated with a 53% to 74% inhibition of tumor growth rate." Fourteen patients with stage IIIB and stage IV non-small cell lung cancer who added FSV to their daily diet for 2 to 46 months were also evaluated. According to Sun et al, "the lead case remained tumor free for more than 133 months; the second case showed complete regression of multiple brain lesions after using FSV and radiotherapy. The median survival time of the remaining 12 patients was 33.5 months and one-year survival was greater than 70%." Ultimately, Sun et al concluded that not only was ingesting FSV nontoxic, but its ingestion was also "associated with objective responses, prolonged survival, and attenuation of the normal pattern of the progression of stage IIIB and stage IV of non-small cell lung cancer."

Though these results appear promising (as do the results of the previous 1999 clinical trial by Sun et al), the results should be viewed with some degree of caution, because more research is needed. For example, in order to confirm the results of the 2001 study, a large randomized controlled clinical trial should be conducted. Furthermore, as the National Cancer Institute points out, "all of the patients [in the 2001 study] were aware of the reported benefits of Sun's soup and had actively sought treatment." Therefore, the National Cancer Institute states cautions that "the results obtained with such highly motivated, self-selected patients might not be typical of those obtained with most patients diagnosed with advanced non-small cell lung cancer." In addition, both the 1999 and 2001 Sun et al studies share a weakness: the small number of patients involved. Another problem is that the formulations in both studies differ, making a comparison between the two difficult. Therefore, more studies testing both formulations on larger samples sizes are needed to confirm the results.

Recommended dosage

Patients should consult their physicians for dosage clarification, including how much and how often any dietary supplement should be taken, as well as the best formulation to use. For example, in the study conducted by Sun et al that was published in *Nutrition and Cancer* in 1999, the mixture tested was in the freeze-dried powder form and the participants orally consumed 30 grams of it a day, which they mixed with water or soup. In the subsequent study conducted by Sun et al that was published in *Nutrition and Cancer* in 2001, the participants orally consumed 10 ounces a day, which is approximately 283 grams, of the reformulated, frozen mixture. Both forms are available in the United States, but consumers should be aware that dietary supplements are not regulated by the United States Food and Drug Administration. Therefore, Sun's soup should be purchased only from a reputable supplier, preferably one who is recommended by a physician.

QUESTIONS TO ASK THE DOCTOR

- What is the most likely cause of my SVC syndrome?
- What tests will be done to determine the cause of my SVC syndrome?
- What are my treatment options for SVC syndrome?
- Am I a candidate for a stent?
- If I am a candidate for thrombolytic therapy, will ongoing anticoagulation be used? Will it interfere with my cancer therapy?
- If I choose to do nothing (opt for no therapy), what may be the consequence?
- Is my SVC syndrome presenting an oncologic medical emergency?

Precautions

Patients should consult with their physician regarding all food or over-the-counter medications before they are consumed.

The National Cancer Institute indicates that there is no information on the safety or the efficacy of this treatment.

Side effects

No toxic side effects are known to be associated with the use of Sun's soup. A bloated sensation was reported by participants in the 1999 study conducted by Sun and colleagues. Participants in the 2001 study did not experience any negative side effects. However, an important distinction between the two studies should be noted. In the 1999 study, the mixture of Sun's soup was in a freeze-dried powder form and was mixed with water or soup. In the 2001 study, a reformulated, frozen mixture of Sun's soup was used. This difference could explain why the participants reported different responses.

Interactions

Although Sun's soup is not known to interact with other medications, it is best for patients to consult a pharmacist and/or physician regarding the safety of its use.

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Other

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Lee Ann Paradise

Superior vena cava syndrome

Definition

The superior vena cava is a large vein in the chest that drains the blood from the upper body back to the heart. Compression or occlusion (blocking off) of this vein creates superior vena cava syndrome.

Description

When the superior vena cava (SVC) becomes compressed or occluded, the blood from the upper body cannot drain back to the heart properly. This creates suffusion (the spreading of bodily fluids into surrounding tissue) which causes varying degrees of airway obstruction, swelling and cyanosis (purple discoloration due to lack of oxygenation) of the face, neck, arms and chest area.

Causes

Cancer is the most common cause of superior vena cava Syndrome. Lung cancer, **lymphoma**, **breast cancer**, and **germ cell tumors** of the chest are commonly associated with SVC syndrome. Any cancer that invades or constricts the blood vessels in the chest can cause SVC syndrome. Other non-cancer causes of SVC

Syndrome are thyroid goiter, fungal infections, pericardial constriction, aortic aneurysm, and any other disease that creates swelling in the mediastinum (organs and vessels of the chest). Occasionally, SVC syndrome can be caused by a central vein catheter (an IV catheter that is placed into central circulation with its tip in the superior vena cava), which may cause a thrombosis (blockage) of the SVC.

Symptoms

Patients with superior vena cava syndrome (SVC syndrome) might experience facial swelling causing the shirt collar to feel tight, shortness of breath, coughing, a change of voice, or confusion. A patient might also notice distention or enlargement of veins near the surface of the skin. The development of these signs and symptoms is usually a gradual process taking up to four weeks from onset of symptoms to diagnosis.

Diagnosis

The physician diagnoses SVC syndrome by starting with a complete patient history and physical examination. The physician will ask about onset of symptoms and timeframes of symptom development. The physician will recommend a chest x ray and a computed tomography scan to visualize the chest area in order to confirm the presence of SVC syndrome. The physician may also order venous patency (flow of blood through the vein) studies using contrast dye and scanning techniques. The physician may order a scan done in a **Magnetic resonance imaging** (MRI) lab, ultrasound lab, or in nuclear medicine to help assess the cause of the superior vena cava syndrome. These tests help the physician identify the site and nature of the obstruction. If cancer of the bronchi is suspected, the patient should also anticipate other testing such as sputum collection, **bronchoscopy**, and **biopsy** of the suspected cancer site. These tests are very important to the oncologist (a physician who specializes in the treatment of cancer), because they will help to identify the disease, determine the stage, and hence the appropriate course of treatment.

Risks

Many patients have the symptoms of superior vena cava syndrome for more than a week before seeing their doctor. Sometimes the diagnosis of SVC syndrome is the first sign that there is cancer present in the body (only 3% to 5% of patients with SVC syndrome do not have cancer). Most patients with SVC syndrome do not die from the syndrome itself, but from the underlying disease, and the extent of the cancer invasion causing the syndrome. Physicians consider the presence of superior vena cava syndrome a life-threatening oncologic medical emergency when there is tracheal (airway) obstruction present. Further, if there is extensive suffusion causing swelling in the vessels in the brain, the patient's condition can rapidly deteriorate. Once the diagnosis of SVC syndrome is made, the physician will immediately commence determining the cause of the syndrome to avoid or minimize these risks.

KEY TERMS

Adjunctive therapy—Sometimes referred to as "secondary therapy," adjunctive therapy is used in conjunction with the primary therapy.

Beta-glucan—Found in a variety of mushrooms, beta-glucan is a type of polysaccharide believed by some researchers to contain anti-tumor properties and the ability to boost the immune system.

Bioavailability—The ability of a drug to be absorbed and used by the body.

Hedyotis diffusa—In ancient Chinese medicine, this herb has been used to boost the immune system.

Median survival time—The National Cancer Institute defines median survival time as "the time from either diagnosis or treatment at which half the patients with a disease are found to be, or expected to be, still alive." With regard to a clinical trial, median survival time is a common measurement used to determine the effectiveness of a treatment.

Non-small cell cancer—The National Cancer Institute defines non-small cell cancer as "a group of lung cancers, which includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma."

Scutellaria barbata—Commonly used in traditional Chinese medicine to treat lung cancer, Scutellaria barbata is an herb that belongs to the skullcap family.

Stage I non-small cell cancer—The National Cancer Institute defines this stage as "cancer [that] is present in the lung only. Stage I is also divided into stages IA and IB based on the size and location of the tumor."

Stage III non-small cell cancer—The National Cancer Institute defines this stage "as cancer that has spread to structures near the lung; to the lymph nodes in the area that separates the two lungs (mediastinum); or to the lymph nodes on the other side of the chest or in the lower neck." Stage III is also divided into stage IIIA (resection likely) and stage IIIB (resection unlikely).

QUESTIONS TO ASK YOUR DOCTOR

- Which risk group has my child been assigned to?
- What treatments would you recommend for a child in that group, and why would you recommend them?
- Is my child eligible for any current clinical trials for children with SPNETs?
- Would you recommend any of the treatments currently considered experimental?
- If the tumor recurs, what is my child's life expectancy? What can I do to make the remaining time as pain-free and enjoyable as possible?

Treatment

There are several treatment options to alleviate the symptoms of SVC syndrome. The feasibility of these options depends on the primary cause of the obstruction, the severity of the symptoms, the prognosis of the patient, and the patient's preferences and ultimate goals for therapy. The physician will need to determine the histology (cellular origin) of the obstructing cancer before proceeding with SVC syndrome treatment. Unless there is airway obstruction or swelling in the brain, treatment of SVC syndrome can be delayed to determine the stage of the underlying disease.

Medical management of SVC syndrome includes elevating the head, using steroids to minimize swelling, and diuretics to remove fluid from circulation. Some patient may develop collateral circulation (development of smaller vessel branches to assist with the excess fluid load on the SVC) and not need further treatment.

Chemotherapy is used on lymphomas or small cell lung cancers because they are sensitive to the drugs. Rapid initiation of chemotherapy in these situations can dramatically reduce the unpleasant symptoms of SVC syndrome in most patients. When chemotherapy is not the best choice for the cancer type, **radiation therapy** can provide some relief from symptoms.

Other treatment options include thrombolysis where a fibrolytic agent (agent that breaks down a thrombus or clot) is injected into the obstructed SVC. This option is used when it is determined that the obstruction is inside the vein. Stent placement (placing a sterile mesh tube inside the SVC to keep the vessel open) has been used successfully in some patients, but may require ongoing anticoagulation therapy after placement. Finally, surgical bypass of the obstructed SVC is a possible option for some patients, however the procedure is extensive and the patient must have appropriate healthy veins to graft to the affected area.

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Supratentorial primitive neuroectodermal tumors

Definition

Supratentorial primitive neuroectodermal tumors, or SPNETs, are primary brain tumors found mostly in children. The word *supratentorial* refers to the location of these tumors in the part of the brain called the cerebrum, above the tentorium (the tentlike membrane that covers the cerebellum). This term is used to differentiate these tumors from medulloblastomas, which are sometimes called infratentorial primitive neuroectodermal tumors (IPNETs) because they are located beneath the tentorium. *Primitive* refers to the fact that SPNETs arise from cells that have not yet separated into more specialized types of cells. The word *neuroectodermal* means that these tumors develop out of a layer of cells in the embryo that eventually gives rise to the baby's nervous system. Supratentorial primitive neuroectodermal tumors are also called cerebral neuroblastomas.

Description

SPNETs are rapidly growing tumors that are considered highly malignant. While they resemble medullo-

blastomas in terms of the type of cells that give rise to them, they are far less common; the ratio of medulloblastomas to SPNETs is thought to be about 25: 1.

The location of SPNETs in the cerebrum means that they occur in the largest part of the brain—the portion that governs speech, emotions, voluntary muscular movements, and the ability to think, reason, and solve problems. These tumors may metastasize, or spread, to other parts of the central nervous system (CNS) via the cerebrospinal fluid. A doctor looking at a CT scan of one of these tumors will usually see a large mass with clear margins that contains cysts, calcifications (deposits of calcium within the brain cells), and patches of dead tumor cells. In some cases the doctor will also see evidence of bleeding into nearby tissue.

Demographics

These tumors are extremely rare, accounting for only 0.5–2 percent of childhood tumors of the central nervous system (CNS). About 2200 children below the age of 15 are diagnosed with malignant tumors of the brain and spinal cord each year in the United States; between 10 and 40 of these children will be diagnosed with SPNETs.

It is difficult to evaluate the statistical significance of racial or gender differences in such a small group; however, the available evidence from American cancer registries suggests that these cancers occur more frequently in Caucasian children than in African Americans, and more frequently in males than in females. The male: female ratio is thought to be about 1.8: 1.

SPNETs occur almost exclusively in younger children, with very few cases reported in adolescents or adults. About 75% of these tumors occur in children below the age of 15, with 50% diagnosed in children below the age of 10. Most SPNETs diagnosed in adults occur in young adults between the ages of 21 and 40.

Causes and symptoms

The causes of SPNETs are not well understood as of early 2005. They do not run in families and are not known to be associated with carcinogens in the environment. It is thought that they result from sporadic (random) gene mutations, possibly associated with abnormalities in the short arm of chromosome 17.

The symptoms of a supratentorial primitive neuroectodermal tumor are often insidious, which means that they are gradual in onset. They are caused by the increased pressure of cerebrospinal fluid inside the skull. Depending on the size of the tumor and the child's age, symptoms may include the following:

- headache, usually worse in the morning, sometimes relieved by vomiting
- blurred vision
- nausea and intermittent vomiting
- weakness or loss of sensation on one side of the body
- difficulty with balance
- frequent crying (in children below the age of three)
- decreased interaction with other people
- lowered energy level or unusual need for sleep
- irritability and other personality changes
- unexplained changes in weight or appetite

Parents should note, however, that none of these symptoms are unique to SPNETs; they may be produced by other types of brain tumors, head trauma, meningitis, migraine headaches, or several other medical conditions. In any event, a child with these symptoms should be seen by a doctor at once.

Diagnosis

The diagnosis of a supratentorial primitive neuroectodermal tumor begins with a review of the child's medical history and a thorough physical examination. The child may be given several vision tests if he or she is seeing double or having other visual disturbances. The doctor may notice one or more of the following signs, although none of them are distinctive features of SPNETs:

- Papilledema. Papilledema refers to swelling of the optic disk, usually caused by increased fluid pressure behind the eye.
- Ataxia. This term refers to loss of muscular coordination.
- Nystagmus. This refers to rapid involuntary movement of the eyeball. The doctor may be able to detect it by having the child look to the right or the left.
- Palsy of the lower cranial nerve.
- Dysmetria. This term refers to the loss of ability to estimate distance when using the muscles; an example would be overreaching when trying to pick up a small object.

The child's doctor will then order both laboratory tests and **imaging studies**. The laboratory tests are done to rule out such diseases as meningitis and to see whether the child's liver and other organs are functioning normally. The imaging studies are performed to determine the extent of the cancer and to assign the child to a risk group.

The diagnosis of SPNET cannot be confirmed, however, on the basis of a clinical examination. Instead, a neurosurgeon will perform what is known as an open **biopsy**. He or she will drill a small hole in the child's skull and remove a small piece of the tumor for examination by a pathologist.

Imaging tests

Imaging tests for SPNETs include the following:

- Magnetic resonance imaging (MRIs).
- Computed tomography (CT) scan.
- Chest x-ray.
- Bone scan. This test is necessary to determine whether the tumor has spread beyond the central nervous system.

Laboratory tests

Standard laboratory tests for children with brain tumors include a complete blood count (CBC), electrolyte analysis, tests of kidney, liver, and thyroid function, and tests that determine whether the child has been recently exposed to certain viruses. In addition, a **lumbar puncture** will usually be performed to look for cancer cells in the child's spinal fluid.

Treatment team

Since the 1960s, most children diagnosed with brain tumors have been treated in specialized children's cancer centers. A child with a SPNET will usually have a pediatric oncologist as his or her primary doctor, along with one or more specialists. These specialists may include a neurosurgeon, pathologist, neuroradiologist, radiation oncologist, medical oncologist, endocrinologist, nutritionist, physical therapist or rehabilitation specialist, and psychologist or psychiatrist. The team will also include social workers, clergy, and other professionals to help the parents cope with the stresses of their child's illness and treatments.

Clinical staging, treatments, and prognosis

Staging

Supratentorial primitive neuroectodermal tumors are not staged in the same way as cancers elsewhere in the body. Instead, children with these tumors are divided as of the early 2000s into two risk groups, average risk and poor risk. Assignment to these groups is based on the following factors:

- child's age
- size and location of the tumor
- whether the tumor has spread to other parts of the central nervous system
- whether the tumor has spread beyond the CNS to other parts of the body

Average-risk children are those older than three years, with most or all of the tumor removed by surgery and no evidence that the cancer has spread beyond the cerebrum. Poor-risk children are those who are younger than three years, whose cancer was located near the center of the brain or could not be removed completely by surgery, and whose cancer has spread to or beyond other parts of the CNS. The risk of recurrence is higher for children in the poor risk group.

Treatments

Treatments for SPNETs depend on the child's age and his or her risk group. Children younger than three years are not usually given **radiation therapy** because it can affect growth and normal brain development. They are usually treated with surgery first to remove as much of the tumor as possible, followed by **chemotherapy** if they are considered poor-risk patients. The drugs most commonly used to treat SPNETs include **lomustine**, **cisplatin**, **carboplatin**, and **vincristine**.

In addition to removing the tumor, the surgeon may also place a shunt to reduce pressure on the child's brain if the tumor is blocking the flow of cerebrospinal fluid. A shunt is a plastic tube with one end placed within the third ventricle of the brain. The rest of the shunt is routed under the skin of the head, neck, and chest with the other end placed in the abdomen or near the heart. About 30 percent of children treated for SPNETs require shunt placement.

Children three years and older are treated with surgery first, followed by radiation treatment of the entire brain and spinal cord. Those considered poor risks may also be given chemotherapy. Recurrent SPNETs are treated with further surgery and an additional course of chemotherapy.

Treatments for supratentorial primitive neuroectodermal tumors that are considered experimental as of 2005 include the following:

- Gamma knife surgery (GKS).
- Gene therapy.
- High-dose chemotherapy. Chemotherapy with **topotecan** has been reported to give promising results in treating SPNETs, as does high-dose chemotherapy combined with stem cell transplantation.
- **Photodynamic therapy**.
- **Bone marrow transplantation**.

- Newer drugs: **Irinotecan**, tipifarnib, lapatinib, ixabepilone, cilengitide, and tariquidar.

Prognosis

The prognosis for children with SPNETs depends largely on their risk group. In general, however, these tumors have a poorer prognosis than other types of brain tumors in children, in part because of the difficulty of removing the complete tumor due to its large size, its extensive blood supply, and its location within the cerebrum. The overall five-year survival rate of children with supratentorial primitive neuroectodermal tumors is reported to be 50–60 percent, but is much lower in children younger than three years and in older children who do not respond to radiation therapy.

Recurrent tumors of this type are almost always fatal; there are no effective therapies for recurrent SPNETs as of the early 2000s.

Alternative and complementary therapies

Some complementary therapies that are reported to help children with SPNETs include pet therapy, humor therapy, art therapy, and music therapy. All of these can be pleasurable for the child as well as relaxing. Ginger or peppermint may help to relieve the **nausea and vomiting** associated with chemotherapy.

Coping with cancer treatment

Children being treated for SPNETs can be given additional medications to treat nausea and other side effects of chemotherapy. With regard to homesickness and other emotional reactions to being away from home, childrens cancer centers have social workers and child psychologists who can educate the childs family about the cancer as well as help the child deal with separation issues.

The side effects of radiation therapy in children with brain tumors may include the formation of dead tissue at the site of the tumor. This formation is known as radiation necrosis. It occurs in about 5 percent of children who receive radiation therapy and may require surgical removal. Radiation necrosis, however, is not as serious as recurrence of the tumor.

Children who have difficulty speaking after brain surgery, or who experience physical weakness, difficulty walking, visual impairment, or other sensory problems, are given physical therapy and/or speech therapy on either an inpatient or outpatient basis.

Clinical trials

Because SPNETs are so rare, the American Cancer Society recommends that children diagnosed with these tumors be enrolled in an appropriate clinical trial. As of early 2005, there are about 30 **clinical trials** in the United States for children with various types of PNETs. Some of these trials involve gene testing to improve diagnosis of children with brain tumors, while others are exploring various combinations of chemotherapy (including new agents), photodynamic therapy, stem cell transplantation, and bone marrow transplantation as treatments for primitive neuroectodermal tumors.

KEY TERMS

Blastoma—An abnormal growth of embryonic cells. Supratentorial primitive neuroectodermal tumors are sometimes called cerebral neuroblastomas.

Calcification—A deposit of calcium within cells or tissues. Calcifications in the brain are often visible on imaging studies of SPNETs.

Cerebellum—The part of the brain that lies within the lower back portion of the skull behind the brain stem. The cerebellum helps to coordinate voluntary movements.

Cerebrum—The largest part of the brain in humans, occupying the upper part of the skull cavity. Supratentorial primitive neuroectodermal tumors are located in the cerebrum.

Medulloblastoma—A malignant tumor of the cerebellum that occurs mostly in children and is considered a type of primitive neuroectodermal tumor. Medulloblastomas are sometimes classified as infratentorial primitive neuroectodermal tumors because they develop underneath the tentorium.

Primary brain tumor—A tumor that starts in the brain, as distinct from a metastatic tumor that begins elsewhere in the body and spreads to the brain.

Primitive—Simple or undifferentiated. SPNETs are classified as primitive tumors because they arise from cells that have not yet separated into groups of more specialized cells.

Shunt—A tube inserted by a surgeon to relieve pressure on the brain from blocked cerebrospinal fluid. The tube allows the fluid to bypass the tumor that is blocking its flow.

Supratentorial—Located above the tentorium, which is the tentlike membrane that covers the cerebellum.

Ventricle—One of the small cavities located within the brain.

Prevention

There is no way to prevent SPNETs as of the early 2000s because their cause is still unknown.

Special concerns

Children with SPNETs are like children with other long-term illnesses in that they may develop emotional problems in reaction to restrictions on their activities, uncomfortable treatments, or being treated in a cancer center away from home. These children may withdraw from others, become angry or bitter, or feel inappropriately guilty about their illness. It is important for parents to reassure the child that he or she did not cause the cancer or deserve it as a punishment for being "bad." Parents may benefit from consulting a child psychiatrist about these and other emotional problems.

Another special concern is the task of explaining the childs illness and treatments to other family members and friends in ways that they can understand. Members of the childs treatment team can be helpful in providing simplified descriptions for siblings or schoolmates.

A third area of concern with **childhood cancers** is the parents' relationships with their other children and with each other. Siblings may resent the amount of time and attention given to the child with cancer, or they may fear that they too will develop a brain tumor. Support groups for families of children with cancer can help by sharing strategies for coping with these problems as well as allowing members to express anxiety and other painful feelings in a safe setting.

See also Medulloblastoma; Pineoblastoma.

Resources

BOOKS

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ORGANIZATIONS

American Academy of Child and Adolescent Psychiatry. 3615 Wisconsin Avenue, NW, Washington, DC 20016-3007. (202) 966-7300. Fax: (202) 966-2891. <http://www.aacap.org.>.

American Brain Tumor Association (ABTA). 2720 River Road, Des Plaines, IL 60018. (800) 886-2282 or (847) 827-9910. <http://www.abta.org>. This independent nonprofit association supports research as well as providing patient and family education materials.

CureSearch Childrens Oncology Group (COG) Research Operations Center. 440 East Huntington Drive, P. O. Box 60012, Arcadia, CA 91066-6012. CureSearch is a joint effort of two organizations, the Childrens Oncology Group (COG) and the National Childhood Cancer Foundation (NCCF). The COG conducts research and clinical trials while the NCCF conducts fundraising and advocacy initiatives.

OTHER

American Academy of Child and Adolescent Psychiatry (AACAP). *The Child with a Long-Term Illness*. AACAP Facts for Families #19. Washington, DC: AACAP, 1999.

American Cancer Society (ACS), Cancer Reference Information. *Brain and Spinal Cord Tumors in Children*. <http://documents.cancer.org/144.00/144.00.pdf>.

Rebecca Frey, PhD

Suramin

Definition

Suramin (suramin hexasodium; CI-1003) is a polysulfonated naphthylurea. It is a growth factor antagonist for palliative treatment in hormone-refractory **prostate**

cancer and hormone-responsive metastatic prostate cancer.

Purpose

Suramin has been used for years to combat African sleeping sickness and river blindness but it has also been found beneficial in slowing the progression of prostate cancer. This drug is classified as an antiprotozoal or anthelminitic. In addition to combating prostate cancer, suramin has demonstrated anti-tumor activity against many types of tumors including endometrial, breast, ovarian, and lung cancer. It has a number of important biological functions for cancer treatment; it inhibits a number of growth factors and receptors needed for tumor growth including epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor, and vascular endothelial growth factor. Suramin decreases blood plasma levels of insulin-like growth factors 1 and 2. Suramin also inhibits tumor antigen, DNA synthesis, cell motility, and urokinase activity. It has also demonstrated significant improvements in pain response. In one of the most recent clinical studies, published in 2001, suramin delayed disease progression, by inhibition of prostate-specific antigen levels, thus prolonging survival in prostate cancer patients. This study also demonstrated suramin delayed two other clinical study endpoints: progression-free survival (i.e. delaying disease progression) and time to pain progression.

Description

While conducting research into suramin as a potential anti-HIV agent, it was found that tumors regressed in HIV-associated cancers. This discovery led investigators to evaluate the antineoplastic effects of suramin. Unfortunately, suramin did not prove effective as an anti-HIV agent.

Suramin, under the brand name Metaret, was submitted for Food and Drug Administration (FDA) approval for treatment of hormone-refractory prostate cancer in 1997 by Warner-Lambert. However, a review by the Oncologic Drugs Advisory Committee in 1998 did not support FDA approval. It was given approval for the "List of Orphan Designations and Approvals." It has been reported to be under development by the Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) and the National Institute of Health (NIH). This drug was withdrawn in 2000 and will not be pursued for FDA approval by Pfizer, who merged with Warner-Lambert.

Recommended dosage

Since this drug is not FDA approved for cancer treatment, dosing information is not readily obtainable. Original research on suramin with continuous infusions was associated with severe toxicities. Due to these toxicities, a long half-life, and a narrow therapeutic range, there was a desire to avoid prolonged continuous infusions. During **clinical trials**, outpatient doses of suramin were aimed at maintaining plasma concentrations at 150 to 250 mcg/mL for three months' duration to minimize treatment exposure.

Precautions

The majority of the precautions listed below are based on suramin's use as an antiprotozoal agent. The following precautions should be considered:

- Allergies. Alert the doctor if any unusual or allergic reaction to suramin occurs or to any other substances, such as foods, preservatives, or dyes.
- Pregnancy. Suramin has not been studied in pregnant women, but animal studies in animals have shown that suramin may cause birth defects or death of the fetus. Before receiving this medicine, alert the doctor if you are pregnant or if you may become pregnant.
- Breast-feeding. It is not known whether suramin passes into breast milk. This issue should be discussed with a doctor for a mother who wishes to breast-feed.
- Children. Suramin can cause serious side effects in any patient, so prior to adminstration to children, discuss the risks with a doctor.
- Older adults. Elderly people are especially sensitive to the effects of suramin. This may increase the chance of side effects during treatment.
- Other medical problems. The presence of other medical problems may affect the use of suramin. Make sure to tell the doctor about any other medical problems, especially kidney or liver disease. Patients with kidney or liver disease may have an increased chance of side effects

Due to a risk of adrenal insufficiency (which results from the inadequate production of adrenal hormones) and coagulopathy (a defect that interferes with the blood clotting mechanism), patients receiving suramin should be administered hydrocortisone and vitamin K.

Significant toxicities are associated the use of suramin. However, with careful monitoring of serum concentrations, these toxicities are manageable.

Side effects

Rash, edema, and asthenia are commonly reported, but generally mild to moderate. Malaise and

KEY TERMS

Antagonist—A drug that binds to a cellular receptor for a hormone, neurotransmitter, or another drug. Antagonists block the action of the substance without producing any physiologic effect itself.

Antineoplastic—Antineoplastic therapy is a regimen of chemotherapy aimed at destroying malignant cells using a variety of agents that directly affect cellular growth and development.

Antiprotozoal—An agent destructive to protozoa.

Anthelmintic—An agent destructive to worms. Many anthelmintic drugs are toxic and should be given with care; the patient should be observed carefully for toxic effects after the drug is given.

Clinical trials—Highly regulated and carefully controlled patient studies, where either new drugs to treat cancer or novel methods of treatment are investigated.

DNA—Deoxyribonucleic acid. Genetic information carried in chromosomes.

Growth factors—Growth factors or human growth factors are compounds made by the body that function to regulate cell division and cell survival. Some growth factors are also produced in the laboratory by genetic engineering and are used in biological therapy. Growth factors are significant because they can induce angiogenesis, the formation of blood vessels around a tumor. These growth factors also encourage cell proliferation, differentiation, and migration on the surfaces of the endothelial cells.

Metastatic—The term used to describe a secondary cancer, or one that has spread from one area of the body to another.

Palliative—To alleviate disease without curing it.

Tumor—An abnormal mass of tissue that serves no purpose. Tumors may be either benign (non-cancerous) or malignant (cancerous).

fatigue are the most common dose-limiting toxicities, affecting 41% of patients in clinical trials for prostate cancer. The majority of the side effects listed below are based on suramin's use as an antiprotozoal agent. Different doses used for cancer treatment may effect the side effect profile. Abdominal pain, **fever**, metallic taste, and a general feeling of discomfort may be bothersome but do not usually require medical attention. These effects may disappear during treatment as the body adjusts to the medicine. Other common side effects are: cloudy urine; crawling or tingling sensation of the skin; **diarrhea**; faintness (particularly after missing meals); headache; increased skin color; irritability; **itching**; joint pain; loss of appetite (anorexia); nausea and vomiting; numbness or weakness in arms, hands, legs, or feet; stinging sensation on skin; swelling on skin; tenderness of the palms and the soles; and becoming easily tired.

Less common side effects may include: extreme fatigue or weakness; increased sensitivity of eyes to light; changes in or loss of vision; watery eyes; swelling around eyes; ulcers or sores in mouth; as well as painful and tender glands in the neck, armpits, or groin.

Side effects that may occur rarely include:

- cold and clammy skin
- convulsions
- decreased blood pressure
- difficulty breathing
- fever and sore throat
- fever with or without chills
- increased heartbeat
- loss of consciousness
- pale skin
- pinpoint red spots on skin
- red, thickened, or scaly skin
- swelling and/or tenderness in upper abdominal or stomach area
- swollen and/or painful glands
- unusual bleeding or bruising
- unusual fatigue or weakness
- yellow discoloration of the eyes or skin

Some patients may experience other side effects not listed above. Patients experiencing any other side effects should check with the attending physician.

Interactions

Drug interaction information is not readily available for suramin. However, as with any treatment, patients should alert their doctor to any prescription, over-the-counter, or herbal remedies they are taking in order to avoid possible drug interactions.

Crystal Heather Kaczkowski, MSc.

Syndrome of inappropriate antidiuretic hormone

Description

The syndrome of inappropriate antidiuretic hormone production (SIADH) is a condition in which the body develops an excess of water and a decrease in sodium (salt) concentration, as a result of improper chemical signals. Patients with SIADH may become severely ill, or may have no symptoms at all.

A syndrome is a collection of symptoms and physical signs that together follow a pattern. SIADH is one of the **paraneoplastic syndromes**, in which a cancer leads to widespread ill effects due to more than just the direct presence of tumor.

Normal physiology

The body normally maintains very tight control over its total amount of water and its concentration of sodium. Many organs including the kidneys, heart, and the adrenal, thyroid, and pituitary glands participate in this regulation. One important contribution is the release of a chemical substance, or hormone, by the pituitary gland into the bloodstream. This chemical substance, called antidiuretic hormone (ADH), is also known as arginine vasopressin, or AVP.

The pituitary releases ADH into the bloodstream when receptors in various organs detect that the body has too little water or too high a concentration of salt. ADH then affects the way the kidneys control water and salt balance. ADH causes the kidneys to decrease their output of urine. The body thus saves water by undergoing antidiuresis, that is, not excreting urine.

Simultaneously, the concentration of sodium in the body serum decreases. This decrease results from a second effect of ADH on the kidneys. When the kidneys retain extra water, the existing concentration of sodium in the body decreases slightly as a result of dilution. These functions are all part of the body's extremely precise control over water and salt balance in health.

Abnormal physiology in SIADH

Certain disease states can upset the delicate balance of water and salt in the body. If there is too much ADH in the body, or if the kidneys overreact to the ADH they receive, the body retains excess water and the serum sodium concentration becomes diluted and falls to abnormal levels. The patient with SIADH develops symptoms based on the degree of abnormality in the serum sodium concentration and the speed with which this concentration falls.

Normal serum sodium concentration is 135-145 mEq/L (milliEquivalents of sodium per liter of body fluid). When the sodium concentration is 125–135 mEq/L the patient may have mild nausea, loss of appetite, **fatigue**, headache, or still remain free of symptoms. As the sodium level drops below 120 mEq/L, the patient experiences greater weakness, confusion, sleepiness, vomiting, and weight gain. As the sodium concentration approaches 110 mEq/L, the patient may suffer seizures, coma, and death.

Causes

SIADH has many known causes, some of which particularly relate to cancer or its treatment. These causes include specific types of cancer, drugs used to treat cancer itself, drugs used to treat the effects of cancer, and conditions that arise as a consequence of cancer or its treatment.

Specific types of cancer

SIADH results from numerous different types of cancer. The malignancies known to cause SIADH include:

- **Lung cancer, small cell** type
- Gastrointestinal cancers (**pancreatic cancer, exocrine**; duodenal or stomach cancer)
- Genitourinary cancer (**bladder cancer**, **prostate cancer**, ovarian cancer)
- Lymphoma, including Hodgkin's disease
- Head and neck cancers (**oral cancers**, **laryngeal cancer**, nasopharyngeal cancer)
- Thymoma
- Brain and central nervous system tumors
- Breast cancer
- Melanoma

Certain cancers produce and secrete ADH themselves. This production occurs without regard for the needs of the body. Thus, the kidneys receive repeated signals to save water, even when the body already has a marked excess of fluid. Of all the types of cancer that produce ADH themselves, small-cell lung cancer is by far the most common. Small-cell cancer of the lung is the cause in 75% of cases of SIADH caused directly by a tumor. In some cases, the appearance of SIADH may be the first indication that a cancer exists.

Also, primary or metastatic tumors in the brain may lead to SIADH. SIADH here results from an increase in intracranial pressure (pressure within the head), or from other effects of intracranial disease on the brain. Increased intracranial pressure commonly causes various parts of the brain to work improperly.

Drugs used to treat cancer itself

A variety of drugs used in cancer treatment may lead to SIADH. The mechanism of this effect may be that the

drug causes the abnormal release of ADH, or that the drug makes existing ADH work in a stronger fashion than usual. **Chemotherapy** drugs that cause SIADH include:

- Vincristine, **vinblastine**, **vinorelbine** and other vinca alkaloids (Oncovin, Velban, Navelbine)
- Cyclophosphamide, **ifosfamide**, **melphalan** and other nitrogen mustards (Cytoxan, Ifex, Alkeran)
- Cisplatin (Platinol-AQ)
- Levamisole (Ergamisol)

Drugs used to treat the effects of cancer

SIADH may occur as a reaction to drugs used to treat effects of cancer such as pain, **depression**, or seizures. SIADH also may result from general anesthesia.

- Narcotic pain medications (morphine, Oramorph SR, fentanyl, Duragesic)
- Tricyclic antidepressants (**amitriptyline**, Elavil)
- Carbamazepine (Tegretol)
- General anesthetics

Conditions that arise as a consequence of cancer

SIADH may result from some of the debilitating consequences of cancer. For example, a person with cancer who is weak or unsteady will have a tendency to fall and hit the head. Skull fracture and other types of head injury may damage the brain or increase the intracranial pressure, and thus lead to SIADH.

Also, cancer patients who are weak, malnourished, receiving chemotherapy, or spending excessive time in bed have an increased risk of **pneumonia** and other infections. Infections including pneumonia, meningitis, and tuberculosis can cause SIADH.

Treatments

The treatment of SIADH involves relief of the urgent symptoms and correction of the underlying problem. For immediate improvement, all patients with SIADH require sharp restriction of their daily water intake. As little as two cups of liquid, about 500 ml, may be the daily limit for some patients. In cases where the sodium concentration is already dangerously low, doctors may cautiously give an intravenous infusion of fluid with a high concentration of sodium (hypertonic saline solution). However, this treatment carries some risk of damaging the brain. Physicians may also use a medicine such as furosemide (Lasix) that promotes water excretion (diuresis). Another drug, **demeclocycline**, blocks the action of ADH in the kidney.

The most definitive way to relieve SIADH is to address the underlying problem itself. Thus, if a tumor produces abnormal ADH, then surgery, **radiation therapy**, or chemotherapy may help by reducing tumor size. If SIADH results from use of a drug, then the patient must discontinue the medicine. Finally, doctors try to identify and treat any other correctable cause, such as an infection.

KEY TERMS

Antidiuretic hormone (ADH)—A chemical hormonal signal sent by the pituitary gland to the kidneys through the bloodstream, telling the kidneys to conserve water in the body.

Diuresis—The excretion of urine.

Hormone—A chemical signal released into the bloodstream that affects one or more other organs.

Hypertonic saline solution—Fluid that contains salt in a concentration higher than that of healthy blood.

Intracranial—Within the head.

Pituitary gland—A small organ, located at the base of the brain, that regulates many body functions.

SIADH—Syndrome of inappropriate antidiuretic hormone production

Serum—The clear yellowish liquid part of whole blood, after it is separated into solid and liquid components. It may be found within the vascular system or in body tissue itself.

Syndrome—A collection of symptoms and physical signs that together follow a pattern.

Prognosis

The prognosis of SIADH depends largely on its cause. Until recently, many physicians believed that the appearance of SIADH indicated a poor prognosis for cancer. However, more recent reports contradict this idea. The patient's ability to observe severe restriction of fluid intake may determine the degree of ongoing symptoms. SIADH usually improves after stopping a drug or curing an infection when that is the cause. When cancer is the direct cause of SIADH, one hopes for similar improvement of SIADH from treatments that reduce the amount of cancer in the body.

Resources

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Kenneth J. Berniker, M.D.

T

Tacrolimus

Definition

Tacrolimus belongs to a group of medicines known as immunosuppressive agents. It is used primarily to lower the body's natural immunity in order to prevent the rejection of organ transplants and to prevent graft-versus-host disease. Tacrolimus is also known as Prograf and FK506.

Purpose

Tacrolimus first saw use in transplant patients. By suppressing the activity of the immune system, tacrolimus makes it more likely that the recipient of a transplanted organ will accept that organ. It is especially used for kidney transplants.

In the fight against leukemia, grafts of stem cells from donors are sometimes given to the patient to encourage the blood of a recipient to begin production of normal cells. Tacrolimus may be given during the graft process because it seems to make the patient more receptive to the donated stem cells.

Description

Tacrolimus somehow suppresses, or prevents activity of, the cells in the lymphatic system, which are known as T cells. Under normal circumstances T cells mount an **immune response** to foreign materials in the body. However, during a transplant, T cells can cause the reaction that can lead to the rejection of a donor organ. The exact reason for the activity of tacrolimus is not understood.

Recommended dosage

Given by mouth, in a capsule, or by intravenous line, tacrolimus doses range from about 0.03 milligrams to 0.05 milligrams per kilogram (1 kilogram equals approximately 2.2 pounds) of body weight per day. Individuals with liver or kidney problems must be given a lower dose.

KEY TERMS

Intravenous line—A tube that is inserted directly into a vein to carry medicine directly to the blood stream bypassing the stomach and other digestive organs that might alter the medicine.

Lymphatic system—The system that collects and returns fluid in tissues to the blood vessels and produces defensive agents for fighting infection and invasion by foreign bodies.

Stem cell—Cell that gives rise to a lineage of cells. Particularly used to describe the most primitive cells in the bone marrow from which all the various types of blood cell are derived.

Precautions

Tacrolimus should be taken without food and long after a meal. If there is food in the stomach it will interfere with the way the drug makes its way into the body. Grapefruit juice can increase the activity of tacrolimus and should be avoided.

Side effects

Many serious side effects are associated with tacrolimus. Conditions affecting the brain brought on by the use of tacrolimus include coma (unconscious state) and delirium (uncontrolled and erratic conscious state). Most times the brain conditions are reversible. Headache, skin rashes, hair loss (**alopecia**), pain, sensitivity to light and shock (anaphylaxis) are all side effects. Kidney damage, which cannot be reversed, is also a danger.

Use of tacrolimus greatly increases the likelihood a person will get skin cancer and **lymphoma**. Anyone

using the drug should be monitored closely for changes in the skin, and all normal precautions for avoiding skin cancer, such as avoiding direct exposure to ultraviolet light, should be taken.

Interactions

This drug interacts with a long list of other drugs. It is important to tell the physician in charge of the care plan, each and every drug being taken, so that interactions can be avoided. Tacrolimus prevents effective vaccination, and vaccinations should not be given while the drug is in use.

Diane M. Calabrese

Tamoxifen

Definition

Tamoxifen (also known as Nolvadex) is a synthetic compound similar to estrogen. It mimics the action of estrogen on the bones and uterus, but blocks the effects of estrogen on breast tissue.

Purpose

Tamoxifen is used as adjuvant hormonal therapy immediately after surgery in early stages of **breast cancer** and in advanced metastatic breast cancer (stages III and above) in women and men. Adjuvant therapy is treatment added to curative procedures (such as surgery) to prevent the recurrence of cancer. Although tamoxifen is also used to treat malignant **melanoma**, brain tumors and uterine cancer, these uses are not indicated on the product label. According to U.S. Food and Drug Administration (FDA) guidelines, women who are at high risk of developing breast cancer may take tamoxifen to reduce their risk; however, prolonged use may increase the risk of developing **endometrial cancer** (also called uterine cancer).

In 2003, researchers described the use of high-dose tamoxifen, along with follicle-stimulating hormone (FSH) in stimulating ovary production for women who have had breast cancer who want to undergo in vitro fertilization. Standard in vitro therapies can increase estrogen and risk of breast cancer recurrence. The combination of tamoxifene and FSH may offer some breast cancer protection and hope for pregnancy.

Description

First synthesized in 1966 in Great Britain as an antifertility drug, tamoxifen was evaluated to treat cancer in 1970. In 1998, the FDA approved tamoxifen to reduce the risk of breast cancer. While tamoxifen can be given to patients alone, it is often given in combination with other chemotherapeutic drugs such as 5-fluorouracil (5-FU, or fluorouracil).

Tamoxifen belongs to a family of compounds called **antiestrogens**. Antiestrogens are used in cancer therapy to inhibit the effects of estrogen on target tissues. Estrogen is a steroid hormone secreted by the female ovary. Depending on the target tissue, estrogen can stimulate the growth of female reproductive organs and breast tissue, play a role in the female menstrual cycle, and protect against bone loss by binding to estrogen receptors on the outside of cells within the target tissue. Antiestrogens act selectively against the effects of estrogen on target cells in a variety of ways, thus they are called selective estrogen receptor modulators (SERMs).

Tamoxifen selectively inhibits the effects of estrogen on breast tissue, while selectively mimicking the effects of estrogen on bone (by increasing bone mineral density) and uterine tissues. These qualities make tamoxifen an excellent therapeutic agent against breast cancer. Although researchers are unclear about precisely how tamoxifen kills breast cancer cells, it is known to compete with estrogen by binding to estrogen receptors on the membrane of target cells. This limits the effects of estrogen on breast tissue. Tamoxifen also may be involved in other anti-tumor activities affecting oncogene expression, promotion of apoptosis (cancer cell death) and growth factor secretion. (Growth factors are hormones that influence cell division and proliferation, and these hormones can encourage cancers to grow.)

In 2000, the STAR (Study of Tamoxifen and **Raloxifene**) study began. The purpose of this double-blind study is to evaluate the use of tamoxifen and raloxifene (another type of SERM) over a five-year period in 22,000 postmenopausal women 35 years or older who are at high risk for developing breast cancer. The study will evaluate both the effectiveness and degree of side effects to determine which drug is most beneficial.

Another National Cancer Institute study that is relevant to the discussion of tamoxifen is the Breast **Cancer Prevention** Trial. This trial began in 1992 and was designed to see if tamoxifen was effective as a preventive against breast cancer. The study also was a double-blind study, and participants were receiving either tamoxifen or a placebo (an inactive pill that looks like tamoxifen). About four years into the study, in 1998, researchers reported that the women receiving tamoxifen:

- had 49% fewer diagnoses of invasive breast cancer
- had 50% fewer diagnoses of noninvasive breast cancer (such as ductal **carcinoma** in situ)

- had fewer fractures of the hip, wrist, and spine
- had more than twice the chance of developing endometrial cancer, and
- had increased chance of developing blood clots, both in the lung and in major veins when compared to the women receiving the placebo. Because of these findings, in 1998, the FDA approved the use of tamoxifen as a breast cancer preventive for high-risk women, as mentioned above.

Recommended dosage

Tamoxifen is taken orally and is available in 10- and 20-milligram (mg) tablets. Although it can be given within the range of 10 mg to 80 mg, the typical dosage is 20 to 40 mg daily for both adult females and males using tamoxifen for treatment of advanced breast cancer. At this dosage, there is an observed 30% response rate with complete remission in 10% of patients. It appears that patients 60 years and older have higher response rates. For patients using tamoxifen for adjuvant therapy after surgery, the typical dosage is 20 mg once daily for two to five years following surgery. Women at high risk for developing breast cancer usually take 20 mg daily for five years. If a dosage is missed, patients should not double the next dosage. Instead, they should go back to their regular schedule and contact their doctor.

Tamoxifen doesn't work for everyone. In 2003, scientists announced development of a new test that may predict whether patients' tumors are responding to tamoxifen treatment and warn clinicians if the tumor becomes resistant to the drugs.

Precautions

Tamoxifen is not recommended for use in children. Women who are pregnant or nursing should not use this drug since it has several side effects that, although rare, can be severe. It is known to cause miscarriages and birth defects. Women are encouraged to use birth control while taking tamoxifen. However, oral contraceptives can negatively alter the effects of tamoxifen. Therefore, patients should explore other, nonhormonal birth control options.

Great care should be exercised when tamoxifen is used with **warfarin**, an anticoagulant, because tamoxifen can interfere with the effects of warfarin, and dose adjustments may be necessary. Patients who are predisposed to the formation of thromboembolisms, or blood clots, should use tamoxifen with caution. It should be noted that smokers are at a higher risk for thromboembolism than nonsmokers.

KEY TERMS

Anticoagulant—An agent preventing the coagulation (clotting) of blood.

Apoptosis—A type of cell death where cells are induced to commit suicide.

Double-blind study—A study where neither the participant nor the physician know who has received the drug in question.

Oncogene—A gene whose presence can cause cancer; usually arising through mutation of a normal gene.

Thromboembolism—A blood clot that blocks a blood vessel in the cardiovascular system.

In late 2003, cancer experts were beginning to recommend a new group of drugs called aromatase inhibitors (Arimidex, common name anastrozole or Femara and Novartis, common name letrozole) as an alternative to tamoxifen or following tamoxifen therapy. These drugs fight breast cancer differently, but early research shows they fight it as effectively and with fewer side effects. However, these drugs also may be added after a course of tamoxifen to improve overall treatment results.

Side effects

Although tamoxifen is usually well tolerated by patients, there are some side effects. About 25% of patients experience side effects such as mild nausea, vomiting, hot flashes, weight gain, **bone pain**, and hair thinning. These side effects are usually not severe enough to stop therapy. Patients using tamoxifen for long periods of adjuvant therapy may face unwanted effects years into therapy, which warrant discontinued use of the drug. Some of these effects include possible increased risk of developing liver **adenoma** as well as increased risk of uterine (endometrial) cancer; eye problems such as retinal lesions, macular edema and corneal changes (most resolve after use is discontinued); neurological problems such as **depression**, dizziness, confusion, and **fatigue**; and genital problems such as vaginal bleeding, vaginal discharge, and endometriosis.

Interactions

Tamoxifen can interfere with the anticoagulant drug warfarin, and if these two drugs are used together, patients will need to be monitored very closely. Oral contraceptives can also interfere with the action of

tamoxifen. In 2003, researchers discovered that paroxetine, an antidepressant used to ease hot flashes that accompany treatment with tamoxifene, was interfering with tamoxifene's effectiveness.

See also Alopecia; Nausea and vomiting; Toremifene.

Resources

PERIODICALS

"Breast Cancer Guidelines Suggest Alternative to Standard Therapy." *Drug Topics* August 18, 2003: 22.

"Drug that Eases Tamoxifen Side Effect May also Hinder its Effectiveness." *Drug Week* December 26, 2003: 54.

Johnson, Kate. "High-dose Tamoxifen for IVF in Breast Cancer Survivors: Combine with FSH." *OB GYN News* December 15, 2003: 8–11.

MacReady, Nora. "Post-tamoxifen Letrozole May Cut Breast Ca Risk: More than 5,000 Women Studied." *Internal Medicine News* November 15, 2003: 18–19.

"New Test Could Predict Response to Tamoxifen and Anastrozole." *Drug Week* November 28, 2003: 64.

Sally C. McFarlane-Parrott
Teresa G. Odle

Taste alteration

Description

Taste alteration refers to a decrease in the ability to taste foods (hypogeusia), changes in how food tastes (dysgeusia), or the complete loss of the ability to taste foods (ageusia). It also refers to the presence of a metallic or medicine-like taste in the mouth. Taste alterations may occur as a result of cancer treatment, infection within the mouth, or the cancer itself.

Taste alteration can have a significant effect on the nutritional status of a cancer patient. Patients with taste alteration may avoid certain foods, lose their appetite (**anorexia**), and lose weight. Eating can be a chore when the patient also has a dry mouth (**xerostomia**) or a mouth infection, such as **thrush**.

Causes

Humans have the ability to taste bitter, salty, sour, and sweet flavors with the taste buds. Taste buds are on the tongue, back portion of the roof of the mouth (soft palate), and the back of the throat. The taste buds are composed of taste cells. Taste cells have tiny hairs (microvilli) which take up microscopic particles of food in the mouth. Taste alteration occurs when the taste buds are damaged by cancer therapy or as a symptom of xerostomia or infection.

Taste alteration may be caused by the cancer itself. Invasion of the mouth by the tumor can alter taste. Between 88% and 93% of the patients with head and neck tumors have taste alterations. Cancer can cause the patient to become deficient in nutrients such as copper, niacin, nickel, vitamin A, and zinc, which can lead to taste alterations. In addition, it is believed that cancer-related chemicals in the bloodstream may affect taste.

Taste alteration can occur in patients who are receiving **radiation therapy** to the head, neck, or chest. The taste buds are very sensitive to radiation and taste alteration can occur within the first two weeks of radiation therapy. Also, radiation therapy can cause decreases in the production of saliva, which can alter taste. Reduced amounts of saliva can change the taste of salty and bitter foods.

Patients undergoing **chemotherapy** may experience taste alterations. Chemotherapy drugs damage the taste cells. The resulting alterations in taste are varied but the most common complaints include: a metallic taste, enhanced taste of bitter flavors (such as beef, pork, coffee, chocolate), and reduced taste of sweet flavors. Between 36% and 71% of the patients undergoing chemotherapy experience taste changes. **Antibiotics**, pain relievers (analgesics), antidepressants, and many other drugs can also affect taste. Chemotherapy drugs that are frequently associated with taste changes include:

- carboplatin
- cisplatin
- cyclophosphamide
- dacarbazine
- doxorubicin
- 5-fluorouracil (5-FU, or fluorouracil)
- levamisole
- methotrexate
- nitrogen mustard
- vincristine

Surgery to the head or neck can also cause taste alteration. Metallic or medicine-like tastes can be caused by a zinc deficiency or by increased levels of calcium or lactate.

Taste alteration is usually a temporary condition, although it may take a few months for taste to return to

KEY TERMS

Ageusia—The complete loss of the ability to taste foods.

Dysgeusia—Changes in what food normally tastes like.

Hypogeusia—The decreased ability to taste foods.

Taste buds—Tiny bumps located in several parts of the mouth that enable one to taste foods.

Taste cells—The cells that make up taste buds.

normal. However, surgery of the roof of the mouth (hard palate), tongue, or throat or high-dose radiation therapy can cause permanent taste alteration.

Treatments

There is no cure or treatment for taste alteration. Patients with this condition are counseled on methods to overcome the affect of taste alteration on eating. However, some studies have shown that zinc supplements, given at the first sign of taste alteration, can reduce radiation-induced taste changes.

The patient's teeth should be brushed and flossed before eating to remove old tastes and refresh the mouth. Rinsing the mouth with salted water, water containing baking soda, tea, or ginger ale before eating may be helpful. Brushing and flossing should be performed carefully to prevent damage to the weakened mouth tissues.

There are a variety of measures that can be taken to make food more tasteful and less offensive. Dietary recommendations include:

- eating foods that are cool or at room temperature
- adding tart flavors to foods such as lemon, citrus, and vinegar, unless mouth sores are present
- using mints, gum, or lemon drops to remove bad tastes after eating
- adding more sugar to foods to reduce salty, acid, or bitter tastes
- using barbecue sauce, basil, catsup, chili powder, garlic, mint, mustard, onion, oregano, rosemary, or tarragon to add flavor to foods
- eating frozen fruits such as grapes, melons, or oranges
- eating fresh vegetables, which may taste better than frozen or canned ones

Alternative and complementary therapies

Taste alteration related to a zinc deficiency can be treated by the addition of zinc to the diet. Zinc deficiency can be relieved by taking zinc picolinate supplements. Foods that are rich sources of zinc include oysters, crab, beef, pork, eggs, nuts, yogurt, and whole grains.

See also Sjögren's syndrome.

Belinda Rowland, Ph.D.

Temozolomide

Definition

A **chemotherapy** medicine used to reduce the size of a cancerous tumor and prevent the growth of new cancer cells. In the United States, temozolomide is known by the brand name Temodar and in the European Union as Temodal.

Purpose

Temozolomide is used as a treatment for a type of brain tumor called an anaplastic **astrocytoma**. Specifically, it is a treatment for patients who have experienced a relapse (or recurrence) of this disease while being treated with the drug **procarbazine**, one of a group of anticancer drugs known as nitrosoureas, which include **carmustine** and **lomustine**. As of 2001, it is being investigated as a treatment of newly diagnosed and advanced stages of other brain/central nervous system tumors, such as **oligodendrogliomas** and ependymomas, and for an advanced malignant **melanoma** that has spread to the central nervous system.

Description

Temozolomide was first made in a British laboratory in the early 1980s and was approved for use in the United States in 1999.

It is included in the cancer drug category termed **antineoplastic agents**. These drugs slow or prevent the growth of cancerous tumors. Temozolomide is among a subset of antineoplastic agents that were designed to target rapidly dividing cells in the body, such as the cancerous cells that form tumors. These drugs work by altering the structure of the DNA in fast-growing cells, causing a cell to die or to fail to replicate itself.

The use of temozolomide as a treatment for cancers other than brain cancer and in combination with different

cancer therapies is still experimental. Many ongoing **clinical trials** focus on the use of temozolomide as a cancer treatment not only for newly diagnosed and recurrent brain/central nervous system tumors, but also for advanced stages of **germ cell tumors**, lung cancer (non-small cell), **mycosis fungoides**, **Sézary syndrome**, and **gastrointestinal cancers**. Some clinical trials also involve experimental treatment of advanced brain cancer or malignant melanomas using a combination of temozolomide and other cancer drugs or therapies, such as **radiation therapy** and the drugs interleukin-12, **aldesleukin**, **thalidomide**, carmustine, **interferons**, and lomustine.

It is not yet known if temozolomide is more effective than other treatments, but it has been shown to stop or slow disease progression in patients with recurrent brain tumors who have not responded to other treatments, including other chemotherapy drugs, radiation therapy, or surgery. However, the duration of the response varies.

For the treatment of a malignant melanoma, temozolomide is as equally effective as **dacarbazine**, the drug most frequently used for this cancer. If the cancer spreads to the central nervous system, temozolomide may be more effective than dacarbazine, because it, unlike dacarbazine, is able to move from the blood into the central nervous system.

A possible advantage to the use of temozolomide over other therapy options is that a patient may be able to continue the treatment over a longer period of time. Decreased bone marrow activity (myelosuppression) is a common reaction to many chemotherapy drugs, including temozolomide. But unlike other drugs, this condition is temporary in temozolomide patients; therefore, patients can physically tolerate a more extended treatment. Also, the side effects experienced with temozolomide are usually less severe compared to other drug treatment options, resulting in patients with a better quality of life.

Recommended dosage

Temozolomide is available in capsules and is taken orally. Dosage is determined based on a patient's body height and weight. The typical dose for the first treatment cycle is 150 mg per day taken for five consecutive days, with each treatment cycle lasting 28 days. The number of treatment cycles depends on how well a patient tolerates the treatment and its effectiveness in treating the cancer. The optimal number of treatment cycles is not known.

Because myelosuppression is a common reaction to this drug treatment, white blood cell and platelet counts are carefully monitored, particularly in the first few treatment cycles. A complete blood count is made on day 22 and day 29 of a treatment cycle. If blood counts are below a certain level, treatment is either postponed or the dosage is decreased in the next treatment cycle. The minimum recommended dosage is 100 mg. Blood counts within an acceptable range can result in an increased dosage for the next cycle.

Precautions

Food decreases the rate at which temozolomide is absorbed into the bloodstream. Although there are no foods that should be avoided while taking this drug, it should be taken on an empty stomach and swallowed whole with a glass of water.

Side effects

The most common side effects for patients treated with temozolomide are nausea and vomiting, headache, **fatigue**, and constipation. In a study of 158 brain tumor patients, 53% experienced nausea and 42% experienced vomiting, and most of these cases were moderate, with only about 10% of the patients experiencing severe forms of either condition. Avoiding food prior to taking temozolomide can decrease the occurrence of these effects, or they can be controlled with medication. In the same study, 41% of the patients reported headaches, 34% reported feeling fatigued, and 33% experienced constipation.

Between 10% and 20% of the patients in the study experienced convulsions, partial paralysis, **diarrhea**, **fever**, feeling weak, a infection, dizziness, coordination problems, a **memory change**, or insomnia. Less than 10% of the 158 patients experienced **anorexia**, rash or **itching**, inflammation in the throat region, **incontinence**, back pain, an overactive adrenal gland, anxiety, comprehension problems, coughing, muscle pain, weight gain, **depression**, sinus problems, or abnormal vision.

Myelosuppression is experienced by 4% to 19% of patients. **Neutropenia** and **thrombocytopenia** are the most common forms, and the more severe cases of both are higher in women and in the elderly (patients older than age 70) than in men. When myelosuppression occurs, it usually appears late in the first few treatment cycles and does not worsen over time. On average, blood count levels return to normal 14 days after the lowest blood count is recorded.

Coping with side effects may require making some lifestyle changes or, in some cases, taking medication. For example, to treat constipation, patients may be told to increase the amount of fluid they drink, perform regular exercise, and eat more dietary fiber, while any infection will require medication. Treatment options for side effects should be discussed with a doctor.

KEY TERMS

Anaplasia—Characteristics of a cell, such as shape and orientation, that make it identifiable as a cancer cell.

Anaplastic astrocytoma—The advanced stage of a rapidly growing brain tumor. This type of tumor originates in the brain, unlike other brain tumors that may occur due to the spreading of cancer from another part of the body.

DNA (Deoxyribonucleic acid)—The genetic material found in each cell in the body that plays an important role in controlling many cell functions. When a cell divides to create two new cells, an identical copy of its DNA is found in each. If there is an error in a cell's DNA, division may not occur.

Drug clearance—The amount of a drug that is removed from the body through urination.

Interactions

Valproic acid, a drug used to treat seizures, decreases the clearance of temozolomide from the body by about 5%. No other negative drug interaction has been reported, although its interaction with many conventional and alternative drugs has yet to be studied.

See also Cancer genetics; Chemoprevention; DNA cytometry; Drug resistance; Vaccines.

Monica McGee, M.S.

Teniposide

Definition

Teniposide is a **chemotherapy** medicine used to treat cancer by destroying cancerous cells. Teniposide is also known as the brand name Vumon and may also be referred to as VM-26.

Purpose

Teniposide is approved by the Food and Drug Administration (FDA) as induction therapy (an initial, intensive course of chemotherapy) for refractory childhood acute lymphoblastic leukemia. Teniposide is used in combination with other chemotherapy drugs. It has also been used in some adult leukemias and lung cancers.

Description

Teniposide is a clear liquid for infusion into a vein. Teniposide is a semisynthetic derivative of podophyllotoxin found in extracts of the mandrake plant. It is a member of the group of chemotherapy drugs known as topoisomerase II inhibitors. Topoisomerase II is one of the enzymes involved in rearrangement of DNA structures, such as temporarily breaking DNA strands and resealing them. This process is necessary for cell replication, and topoisomerase II inhibitors interfere with this important process as it prevents the cells from further dividing and multiplying and the cells subsequently die.

Recommended dosage

A teniposide dose can be determined using a mathematical calculation that measures a person's body surface area (BSA). This number is dependent upon a patient's height and weight. The larger the person the greater the body surface area. Body surface area is measured in the units known as square meter (m^2). The body surface area is calculated and then multiplied by the drug dosage in milligrams per square meter (mg/m^2). This calculates the actual dose a patient is to receive.

To treat refractory childhood leukemia

Teniposide is dosed at 165 mg per square meter as an infusion into a vein over 30-60 minutes and is given with the chemotherapy drug **cytarabine** at a dose of 300 mg per square meter. This combination is given twice a week for eight to nine doses.

Other leukemia dosing includes teniposide 100 mg per square meter once or twice weekly, and teniposide 250 mg per square meter with the chemotherapy drug **vincristine** 1.5 mg per square meter given into a vein each week for four to eight weeks.

Patients with significant kidney and liver problems may need to receive a smaller dose of teniposide than patients with normal kidney and liver function.

Patiets with Down syndrome should receive a smaller dose with the initial treatment.

Precautions

Blood counts will be monitored regularly while on teniposide therapy. During a certain time period after receiving this drug, there is an increased risk of getting infections. Caution should be taken to avoid unnecessary exposure to germs. Patients with a known previous allergic reaction to chemotherapy drugs should tell their doctor before treatment. Patients who may be pregnant or trying to become pregnant should tell their doctor before

KEY TERMS

Anemia—Red blood cell count that is lower than normal.

Chemotherapy—Specific drugs used to treat cancer

Refractory cancer—Cancer that is not responding to treatment

DNA—Deoxyribonucleic acid, the genetic material inside cells that allows cells to function, separate, into two cells, and make more cells

Food and Drug Administration—A government agency that oversees public safety in relation to drugs and medical devices. The FDA gives the approval to pharmaceutical companies for commercial marketing of their products

Induction therapy—Initial intensive course of chemotherapy designed to wipe out abnormal cells and allow regrowth of normal cells.

Intravenous—Administered into the body through a vein.

Neutropenia—White blood cell count that is lower than normal.

receiving teniposide. Chemotherapy can cause men and women to be sterile (unable to have children). Patients should check with their doctors before receiving live virus **vaccines** while on chemotherapy.

Side effects

The most common side effect of teniposide is low blood counts, referred to as **myelosuppression**. When the white blood cell count is lower than normal, known as **neutropenia**, patients are at an increased risk of developing a **fever** and infections. Teniposide also causes the platelet count to fall. Platelets are blood cells in the body that allow for the formation of clots. When the platelet count is low patients are at an increased risk for bruising and bleeding. If the platelet count remains too low, a platelet blood transfusion is an option. Low red blood cell counts, referred to as **anemia**, may make patients feel tired, dizzy and lacking energy. A drug known as **erythropoietin** may be given to increase a patient's red blood cell count.

Teniposide infusions given too quickly into the vein can cause a significant drop in blood pressure. This can usually be avoided by administering the drug over a time period of at least 30-60 minutes. Teniposide can also cause mild to moderate **nausea and vomiting**. Patients will be given medicines known as **antiemetics** before receiving teniposide to help prevent or decrease this side effect. **Diarrhea**, loss of appetite (anorexia), and mouth sores and inflammation are also common. Rarely, allergic or anaphylactic-type reactions that include fever, sweating, tongue swelling, chest tightness, **itching**, shortness of breath, low blood pressure and increase heart rate, have occurred.

Other less common side effects caused by teniposide include rash, itching, hair loss (alopecia), liver and kidney problems, fatigue, seizures, tingling, fever, development of another type of cancer or leukemia due to taking the drug, and redness and pain at the site of injection into the vein. All side effects a patient experiences should be reported to their doctor.

Interactions

There is an increase risk of worsening some of the side effects of teniposide when it is administered with the medicines sodium salicylate, tolbutamide (a drug to lower blood sugar levels), or sulfamethizole (an antibiotic).

Nancy J. Beaulieu, R.Ph., B.C.O.P.

Testicular cancer

Definition

Testicular cancer is a disease in which cancer cells are discovered in one or both testicles. The testicles, also known as testes or gonads, are located in a pouch beneath the penis called the scrotum.

Description

The testicles make up one portion of the male reproductive system. Normally, they are each somewhat smaller than a golf ball in size and are contained within the scrotum. The testicles are a man's primary source of male hormones, particularly **testosterone**. They also produce sperm.

There are several types of cells contained in the testicles, and any of these may develop into one or more types of cancer. Over 90% of all testicular cancers begin in cells called germ cells. There are two main types of **germ cell tumors** in men: seminomas and nonseminomas. Seminomas make up about 40% of all testicular germ cell tumors. Nonseminomas make up a group of cancers, which include choriocarcinoma, yolk sac tumors, embryonal **carcinoma**, and teratoma.

Although testicular cancer accounts for less then 2% of all cancers in men, it is the most commonly seen cancer in young men aged 15 to 35. It is also one of the most curable.

Demographics

The American Cancer Society estimates that approximately 8, 980 new cases of testicular cancer will be diagnosed in American men in 2004. In addition, about 360 men will die of the disease during that year. Although the incidence of testicular cancer is rising, having doubled since 1975, it is still rare. Scandinavian countries have the highest rate in the world. Germany and New Zealand also have high rates. The lowest incidences of testicular cancer are in Asia and Africa.

Causes and symptoms

The exact causes of testicular cancer are unknown. However, there is research showing that some men are more likely to acquire it than others. The risk for testicular cancer is much higher for boys born with one or both of their testicles located in the lower abdomen rather than in the scrotum. This condition is called cryptorchidism or undescended testicles. The lifetime risk of getting testicular cancer is four times higher for boys with cryptorchidism than the risk in the general population. This risk factor remains even if surgery is done to place the testicle back into the scrotum.

Boys born with Down syndrome are also at higher risk of developing testicular cancer, although the reasons for this increased risk are not yet fully understood as of 2004.

There are other risk factors as well. Men who have had abnormal development of their testicles are at increased risk, as are men with Klinefelter's syndrome (a disorder of the sex chromosomes). A family history of testicular cancer increases the possibility of getting the disease. Men infected with the human immunodeficiency virus (HIV), especially those with AIDS, have a higher incidence, as do infertile men. Certain testicular tumors appear more frequently among men who work in certain occupations, like miners, oil workers, and utility workers. There is no conclusive evidence that injuries to the testicles, or environmental exposure to various chemicals causes the disease.

Testicular cancer usually shows no early symptoms. It is suspected when a mass or lump is felt in the testes, although a testicular mass does not always indicate cancer and is usually painless.

Symptoms of testicular cancer include:

- a lump in either testicle (usually pea-sized, but may be as large as a marble or an egg)
- any enlargement or significant shrinking of a testicle
- a sensation of heaviness in the scrotum
- a dull ache in the groin or lower abdomen
- any sudden collection of fluid in the scrotum
- tenderness or enlargement of the breasts
- pain or discomfort in a testicle or in the scrotum

Diagnosis

When a man exhibits symptoms that suggest a possibility of testicular cancer, several diagnostic steps will occur before a definitive diagnosis is made.

History and physical

The physician takes a personal and family medical history and a complete physical examination is performed. The doctor will examine the scrotum as well as the abdomen and other areas to check for additional masses.

Imaging studies

If a mass is found, the physician will likely have an ultrasound performed. Through the use of sound waves, ultrasounds can help visualize internal organs and may be useful in telling the difference between fluid-filled cysts and solid masses. If the tumor is solid, it is most likely cancerous.

Computed tomography as well as ultrasound may be used to diagnose malignant germ cell tumors in undescended testes.

Blood tests

Certain blood tests can be helpful in diagnosing some testicular tumors. **Tumor markers** are substances often found in higher-than-normal amounts in cancer patients. Some testicular cancers secrete high levels of certain proteins such as alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and enzymes like lactate dehydrogenase (LDH). These markers may help find a tumor that is too small to be felt during a physical examination. In addition, these tests are also helpful in determining how much cancer is actually present, and in evaluating the response to treatment to make sure the tumor has not returned.

Surgery

If a suspicious growth is found, a surgeon will need to remove the tumor and send it to the laboratory for

testing. A pathologist examines the testicular tissue microscopically to determine whether cancer cells are present. If cancer cells are found, the pathologist sends back a report describing the type and extent of the cancer. In almost all cases, the surgeon removes the entire affected testicle through an incision in the groin, though not through the scrotum. This procedure is called radical inguinal **orchiectomy**.

Once testicular cancer is determined, further tests are necessary to find out if the cancer has metastasized (spread) to other parts of the body, and to ascertain the stage or extent of the disease. This information helps the doctor plan appropriate treatment. These tests may include **computed tomography** (CT scan), **lymphangiography** (x rays of the lymph system), bone scans, and chest x rays.

Treatment team

From diagnosis through treatment and follow-up, several health care professionals participate in the care of the person with testicular cancer. Patients usually seek help from their primary physician after first noticing the lump or other suspicious symptom. A referral to the urologist will follow. The urologist usually performs any diagnostic tests as well as any necessary surgery. A pathologist makes the definitive cancer diagnosis by looking at the cells under a microscope. After the diagnosis is made, the patient will usually see a medical oncologist. If it is determined that **radiation therapy** is appropriate treatment, a visit to the radiation oncologist is recommended as well. Specially trained nurses will administer **chemotherapy** if necessary.

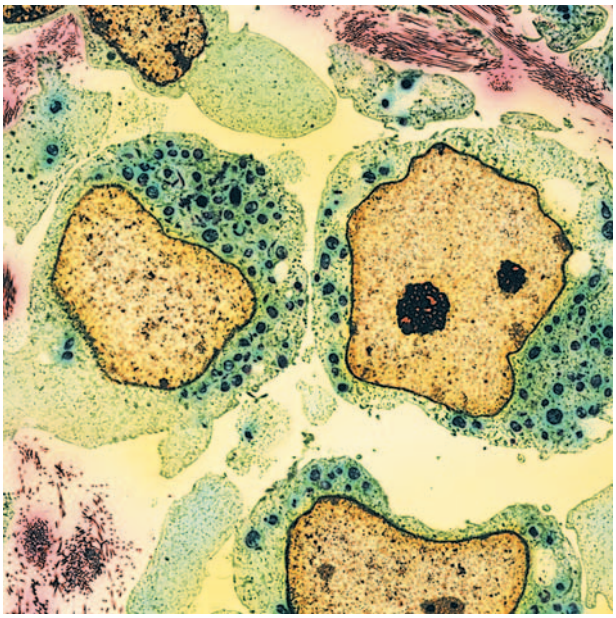
Clinical staging, treatments, and prognosis

Staging

One method the cancer treatment team uses to describe the scope of a patient's cancer is the use of a staging system. Testicular cancer is classified using the TNM system. However, in order to simplify and summarize this information, the TNM description can be grouped according to stages.

Stages of testicular cancer:

- Stage I. This stage refers to a cancer found only in the testicle, with no spread to the lymph nodes or to distant organs.
- Stage II. This indicates that the cancer has spread to the lymph nodes in the abdomen, but not to lymph nodes in other parts of the body.
- Stage III. In this stage, the cancer has spread beyond the lymph nodes in the abdomen, and/or the cancer is in parts of the body far away from the testicles, such as the lungs or the liver.
- Recurrent. Recurrent disease indicates that the cancer has come back after it has already been treated. Testicular cancer can come back in the same testicle (if it was not surgically removed) or in some other body part.



Colored transmission electron micrograph (TEM) of a section through teratoma cancer cells in a testis. Three rapidly dividing cells are seen at center left, center right, and lower right. They have large, irregular nuclei (pale brown) and green cytoplasm. *(Copyright Quest, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Treatment

The treatment decisions for testicular cancer are dependent on the stage and cell type of the disease, as well as the patient's age and overall health. The four kinds of treatment most commonly used are surgery, radiation therapy, chemotherapy, and bone marrow or stem cell transplantation.

Surgery is normally the first line of treatment for testicular cancer and involves the removal of the affected testicle. This procedure is known as a radical inguinal orchiectomy. Depending on the type and stage of the cancer, some lymph nodes may also be removed at the same time, or possibly in a second operation. This procedure is called a retroperitoneal **lymph node dissection**, and can be a major operation. Some patients will experience temporary complications after surgery, including infections and bowel obstruction. If both of the testicles are taken out, a man will have no ability to

produce sperm cells and will become infertile (unable to father a child). Surgery removing the lymph nodes may cause some damage to nearby nerves, which may interfere with the ability to ejaculate. Men undergoing surgery for testicular cancer may wish to discuss nerve-sparing surgery with their doctor, as well as sperm banking.

Radiation therapy for testicular cancer is delivered from a machine and is known as external beam radiation. One potential problem with this type of radiation is that it can also destroy nearby healthy tissue as well as cancer cells. Other potential side effects include nausea, **diarrhea** and **fatigue**. A special device can be used to protect the unaffected testicle to preserve fertility.

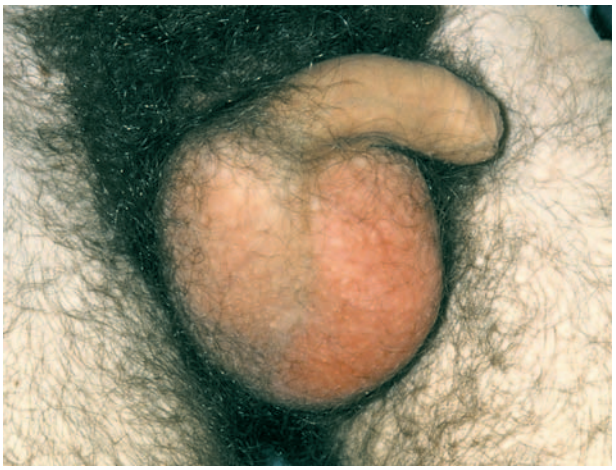
Chemotherapy refers to the use of drugs in treating cancer. Since the drugs enter the bloodstream and circulate throughout the body, chemotherapy is considered a systemic treatment. The drugs primarily used in the treatment of testicular cancer are **cisplatin**, **vinblastine**, **bleomycin**, **cyclophosphamide**, **etoposide**, and **ifosfamide**. These drugs are given in various combinations, since the use of two or more drugs is considered more effective than using only one drug.

Since chemotherapy agents can affect normal as well as cancerous cells, several side effects are possible. These side effects include:

- **nausea and vomiting**
- changes in appetite (anorexia)
- temporary hair loss (alopecia)
- mouth sores
- increased risk of infections
- bleeding or bruising
- fatigue
- diarrhea or constipation

Several drugs are available to assist in treating these side effects, most of which will disappear after the treatment is completed. However, some of the chemotherapy agents used during treatment of testicular cancer may cause long-term side effects. These include hearing loss, nerve damage, and possible kidney or lung damage. Another potentially serious long-term complication is an increased risk of leukemia. This is a rare side effect, however, as it occurs in less than 1% of testicular cancer patients who receive chemotherapy. Chemotherapy may also interfere with sperm production. This may be permanent for some, but many will regain their fertility within a few years.

Studies are ongoing to determine whether high doses of chemotherapy combined with stem-cell transplantation will prove effective in treating some patients with advanced testicular cancer. In this treatment, blood-forming cells called stem cells are taken from the patient (either from the bone marrow or filtered out of the patient's blood). These cells are kept frozen while high-dose chemotherapy is administered. After receiving the chemotherapy, the patient is given the stem cells through an infusion. This treatment enables the use of extra large doses of chemotherapy that might increase the cure rate for some testicular cancers.

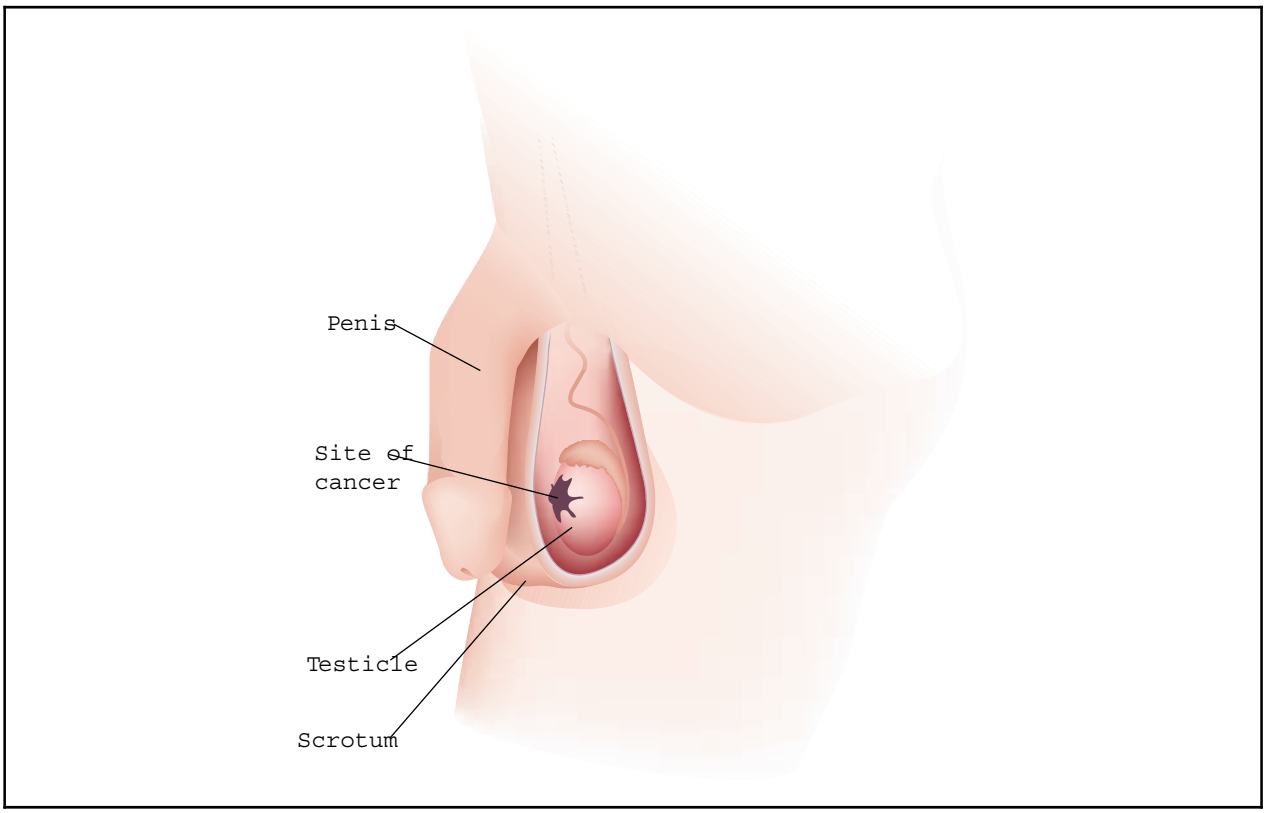


The swollen scrotum of a man suffering from cancer of the testis. *(Copyright Dr. P. Marazzi, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

Preferred treatment plans by stage of disease

Stage I: Stage I seminomas are normally treated with a radical inguinal orchiectomy followed by radiation treatment aimed at the lymph nodes. More than 95% of Stage I seminomas are cured through this method. Another approach is to perform surgery only. Patients are then followed closely for several years with blood tests and **imaging studies**. If the cancer spreads later on, radiation or chemotherapy can still be used. Stage I non-seminomas are also highly curable with surgery, followed by one of three options. These options include the performance of a retroperitoneal lymph node dissection, two cycles of chemotherapy, or careful observation for several years.

Stage II: Stage II seminomas and non-seminomas are cured in 90% to 95% of the cases. For the purposes of treatment, stage II testicular cancers are classified as either bulky or nonbulky. Nonbulky seminomas (no lymph nodes can be felt in the abdomen) are treated with an orchiectomy followed by radiation to the lymph nodes. Men with bulky seminomas have surgery, which may be followed by either radiation or a course of



A cancerous growth on the testicle. *(Illustration by Argosy Publishing Inc. Reproduced by permission of The Gale Group.)*

chemotherapy. Nonbulky Stage II non-seminomas are treated with surgery and lymph node removal, with possible chemotherapy. Men with bulky disease have surgery followed by chemotherapy.

Stage III: Stage III seminomas and non-seminomas are treated with surgery followed by chemotherapy. This produces a cure in about 70% of the cases. Those who are not cured may be eligible to participate in **clinical trials** of other chemotherapy agents.

Recurrent: Treatment of recurrent testicular cancer is dependent upon the initial stage and the treatment given. This might include further surgery and chemotherapy. Many men whose disease comes back after chemotherapy are treated with high-dose chemotherapy followed by bone marrow or stem cell transplantation.

Alternative and complementary therapies

There are currently no scientifically proven alternative treatments known for testicular cancer. Nothing has been shown to be as successful as conventional treatment. However, some patients may find certain alternative or complementary treatments supportive while undergoing surgery, chemotherapy or radiation. For example, meditation and relaxation exercises may prove effective in reducing nausea and vomiting. Some dietary modifications and nutritional supplements may be helpful in assisting with recovery after surgery. The testicular cancer patient considering alternative treatments should talk it over with members of the cancer care team. They may be able to offer additional information.

Coping with cancer treatment

Coping with the effects of cancer treatment can often prove challenging. One of the most common effects of treatment is fatigue. The man going through treatment for testicular cancer should allow time for recovery, and not rush back to normal activities. Eating a balanced diet of healthy foods may be helpful as well. Enlisting friends and family members to aid with transportation and responsibilities at home is another way of coping. Most of the side effects of treatment for testicular cancer can be alleviated. In addition, many men experience some levels of anxiety and/or **depression** during diagnosis and treatment. These can also be treated through medication and/or counseling.

KEY TERMS

Cryptorchidism—A condition that occurs when a boy is born with one or both testicles in the lower abdomen rather than the scrotum. Known also as undescended testicles, it is the primary risk factor for testicular cancer.

Metastatic testicular cancer—Testicular cancer that has spread to other parts of the body.

Radical inguinal orchiectomy—Surgical procedure performed to remove one or both testicles. It is done via a groin incision.

Testicles—Also called testes or gonads, they are part of the male reproductive system, and are located beneath the penis in the scrotum.

QUESTIONS TO ASK THE DOCTOR

- How do I perform a testicular self examination?
- What kind of testicular cancer do I have?
- What treatment choices do I have?
- What side effects can I expect from my treatment?
- How long will it take me to recover?
- What are the chances that the cancer will come back?
- Is there a chance I will become infertile?

Clinical trials

Important research into testicular cancer is ongoing at many medical institutions around the country. Scientists are examining the changes that occur to the DNA of testicular cancer cells, in order to improve their understanding of the causes of the disease, and to find more effective treatments. Clinical trials are a method for doctors to explore new treatment options. For example, stem cell transplantation is being studied as one way to help men with recurrent cancer or a poor prognosis. Various chemotherapy regimens are being tested to find out if changing doses or specific drugs might reduce the incidence of side effects without reducing the effectiveness of treatment. For information on specific clinical trials, patients may ask the cancer care team or get a list of current clinical trials from the National Cancer Institute (see Resources.)

Prevention

The main risk factors associated with testicular cancer—cryptorchidism, family history of the disease, and being Caucasian—are unavoidable since they are present at birth. In addition, many men diagnosed with the disease have no known risk factors. Because of these reasons, it is not possible to prevent most incidences of testicular cancer.

Special concerns

For many men, testicles are symbolic of manhood, and the removal of one can lead to embarrassment, or fear about a partner's reaction. Indeed, after surgical removal, the affected side of the scrotum does look and feel empty. To correct this, a patient can have a testicular prosthesis implanted in his scrotum. This prosthesis looks and feels like a real testicle, and the surgical procedure usually leaves only a small scar.

As of 2004, there is growing evidence that men treated with cisplatin for testicular cancer are at increased risk of coronary artery disease ten years or longer after treatment. In addition, men who have had an orchiectomy followed by external beam radiation therapy have a significantly increased risk of dying from heart disease or a second cancer.

See also Fertility issues; Sexuality.

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Rebecca J. Frey, PhD

Testicular self-exam

Definition

A testicular self-examination (TSE) is the procedure by which a man checks the appearance and consistency of his testes.

Purpose

Most testicular cancers are first noticed by the man himself, many times after a blow or other injury to the scrotum. Men should perform a TSE every month to find out if the testes contain any suspicious lumps or other irregularities, which could be signs of cancer or infection.

It is particularly important for adult male survivors of childhood cancers to perform TSE on a regular basis. A group of researchers at the University of Minnesota reported in 2004 that only 17% of male survivors of childhood cancer examine their own testes as a form of cancer screening. The researchers urged primary care physicians to teach cancer survivors about the importance of regular self-examination in adult life.

Precautions

None.

Description

A TSE should take place during a warm shower or bath, when the skin is warm, wet, and soapy. The man needs to step out of the tub so that he is in front of a mirror. The heat from the tub or shower will relax the scrotum (sac containing the testes) and the skin will be softer and thinner, making it easier to feel a lump. It is important that the exam be done very gently.

The man should stand facing his mirror and look for swelling on the scrotum. Using both hands, the scrotum should be gently lifted so that the area underneath can be checked.

The next step is the exam by hand. The index and middle fingers should be placed under each testicle, with the thumbs on top. The testes should be examined one at a time. The man should roll each testicle between his fingers and thumbs. He should feel for lumps of any size (even as small as a pea) particularly on the front or side of each testicle. He should also look for soreness or irregularities. Next, the epididymis and vas deferens, located on the top and back of the testes, should be felt. This area feels like a cord, and should not be tender.

KEY TERMS

Epididymis—A tube in the back of the testes which transports sperm.

Scrotum—The pouch containing the testes.

Testes (singular, testis)—Egg-shaped male gonads located in the scrotum. Testes is the plural form of testis, which is a testicle.

Vas deferens (plural, vasa deferentia)—A tube that is a continuation of the epididymis. This tube transports sperm from the testis to the prostatic urethra.

Normal results

It is normal for one testicle to be larger than the other, and for them to hang at different levels; but the size should stay the same from one month to the next. The testes should be free from lumps, pain, irregularities and swelling.

Abnormal results

A TSE is considered abnormal if any swelling, tenderness, lumps, or irregularities are found. Hard, unmoving lumps are abnormal, even if they are painless. A lump could be a sign of an infection or a cancerous tumor. A change in testicle size from one month to the next is also abnormal. A feeling of heaviness in the scrotum is another abnormal sign. If any abnormality is found, a man is encouraged to check with his doctor as soon as possible because **testicular cancer** is highly curable if found early.

QUESTIONS TO ASK THE DOCTOR

- How long should a testicular self-examination take?
- What should be done if the presence of a lump is uncertain during a TSE?
- What action should be taken if a lump or abnormality is definitely found during TSE?
- What medical tests are done to confirm testicular cancer?
- How often is a testicular examination performed as part of a physical examination?
- What are the other signs of testicular cancer?

Resources

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Testolactone

Definition

Testolactone is a synthetic drug related to the male hormone **testosterone**. It is used to reduce the size of tumors in some women with advanced **breast cancer**. Testolactone is available in the U.S. under the brand name Teslac.

Purpose

Testolactone is used in treating advanced breast cancer in postmenopausal women and in women who have had their ovaries removed. It is never used in treating breast cancer in men.

Description

Testolactone is approved by the United States Food and Drug Administration (FDA), and its cost usually is covered by insurance. It is classified as an antineoplastic agent, which means that it stops or slows the growth of malignant cells. One advantage of testolactone is that, although it is related to testosterone, it does not cause women to develop male characteristics such as a deep voice or facial hair.

As noted above, testolactone is related to the male hormone testosterone. The way in which it inhibits the growth of breast cancer cells is not clear. However, it is known that the hormone estrogen stimulates the growth of some breast cancer cells, and testolactone seems to interfere with estrogen production. The resulting reduction in estrogen levels may slow the growth of breast cancers sensitive to this hormone.

In breast cancer, testolactone is a palliative treatment. This means that it helps relieve symptoms, but does not cure the cancer. It is effective only in about 15% of the women who take it. In these women, however, it helps reduce the size of half or more tumors. Normally testolactone is used along with other **chemotherapy** drugs for fighting advanced breast cancer.

Recommended dosage

Testolactone comes as a 50 mg tablet. The dose will depend on the patient's body weight and her general health, as well as other drugs she may be taking. However, a standard dose is 250 mg (5 tablets) four times a day for three months. It takes at least several weeks before the drug begins to be effective. Tablets should be stored at room temperature.

Precautions

People with a history of heart or kidney disease should be sure to tell their doctor, as this may affect their use of testolactone.

Side effects

Testolactone often causes nausea, vomiting, and loss of appetite (anorexia). Because testolactone must

KEY TERMS

Malignant—Cancerous. Malignant cells tend to reproduce without normal controls on growth and form tumors or invade other tissues.

Ovaries—A pair of female reproductive organs that release eggs. They are the main source of the female hormone estrogen.

Postmenopausal—Older women who no longer menstruate because of their age.

Testosterone—The main male hormone. It is produced in the testes and is responsible for the development of primary and secondary male sexual traits.

be taken over many months to be effective, people who experience these symptoms should talk to their doctor about medications to relieve the **nausea and vomiting** so that they can continue to take testolactone.

Other side effects reported with testolactone include numbness or tingling in the toes, fingers, and face, **diarrhea**, swelling and water retention in the feet and legs, and swelling of the tongue, hair loss (alopecia), and abnormal nail growth. However, since women who take this drug are receiving other chemotherapy drugs and are in an advanced stage of cancer, it is difficult to pinpoint whether testolactone is exclusively responsible for some of these side effects.

Interactions

Many drugs interact with nonprescription (over-the-counter) drugs and herbal remedies. Patients should always tell their health care providers about these remedies, as well as any prescription drugs they are taking. Patients should also mention if they are on a special diet such as low salt or high protein. They should not take calcium supplements, since testosterone already has the potential to increase circulating calcium to dangerous levels.

Testolactone may increase the effect of anticoagulants (blood thinning medication). In women where cancer has spread to the bones, testolactone may increase the circulating level of calcium in the body. Calcium levels need to be tested regularly.

Tish Davidson, A.M.

Testosterone

Definition

Synthetic derivatives of the natural hormone testosterone are used to reduce the size of hormone-responsive tumors.

Purpose

Testosterone-related drugs are used to treat advanced disseminated **breast cancer** in women.

Description

Testosterone belongs to a class of hormones called androgens. These are male hormones responsible for the development of the male reproductive system and secondary male sexual characteristics such as voice depth and facial hair. Testosterone is normally produced by the testes in large quantities in men. It also occurs normally in smaller quantities in women.

Several man-made derivatives of testosterone are used to treat advanced disseminated breast cancer in women, especially when cancer has spread to the bones. The most common of these testosterone-like drugs are **fluoxymesterone** (Halotestin) and methyltestosterone (Testred). These androgens are used only in women who have late-stage breast cancer and who meet specific criteria. These criteria include:

- The patient is postmenopausal.
- The tumors have been shown to be hormone-dependent.
- The tumors have spread, often to the bone, or recurred after other hormonal cancer treatments.

Using testosterone derivatives to treat breast cancer is a palliative treatment. This means that the treatment helps relieve symptoms but does not cure the cancer. These drugs are approved by the United States Food and Drug Administration (FDA), and their cost is usually covered by insurance.

Clinical trials are currently underway that involve the use of testosterone-related androgens in varying combinations with other drugs to treat advanced cancers. The selection of clinical trials changes constantly. Current information on the availability and location of clinical trials can be found at the following web sites:

- National Cancer Institute. (800) 4-CANCER or <http://cancertrials.nci.nih.gov>.
- National Institutes of Health Clinical Trials. <http://clinicaltrials.gov>.

KEY TERMS

Hormone—A chemical produced by a gland in one part of the body that travels through the circulatory system and affects only specific receptive tissues at another location in the body.

Postmenopausal—Women have stopped menstruating, usually because of their age.

Testes—Egg-shaped male sexual organs contained in the scrotum that produce testosterone and sperm.

- Center Watch: A Clinical Trials Listing. <http://www.centerwatch.com>.

Recommended dosage

Dosage is individualized and depends on the patient's body weight and general health, as well as the other drugs she is taking and the way her cancer responds to hormones. Halotestin comes in tablets of 2 mg, 5 mg, or 10 mg. A standard dose of Halotestin for inoperable breast cancer is 10 to 40 mg in divided doses daily for several months. Tablets should be stored at room temperature. Testred comes in 10 mg capsules. A standard dose for women with advanced breast cancer is 50 to 200 mg daily.

Precautions

Women who take testosterone derivatives for advanced breast cancer are postmenopausal, so the usual precautions about avoiding pregnancy when receiving androgen therapy do not apply.

Side effects

The most serious side effect of these drugs is **hypercalcemia**, a condition in which too much calcium circulates in the blood. This occurs because these drugs liberate calcium from bones. Calcium levels are monitored regularly, and the drug is discontinued if hypercalcemia occurs. Another serious (but less common) side effect is the development of tumors in the liver. Other side effects include deepening of the voice, development of facial hair and acne, fluid retention, and nausea.

Interactions

As with any course of treatment, patients should alert their physician to any prescription, over-the-counter, or herbal remedies they are taking in order to avoid harmful drug interactions. Patients should also mention if they are on a special diet, such as low salt or high protein. They should not take calcium supplements, since testosterone already has the potential to increase circulating calcium to dangerous levels.

Testosterone derivatives may interact with anticoagulant drugs (blood thinners) such as Coumadin.

Tish Davidson, A.M.

Tetrahydrocannabinol

Definition

Tetrahydrocannabinol (THC) is the main psychoactive substance found in the hemp plant *Cannabis sativa*, or marijuana.

Purpose

A number of studies indicate medical benefits of THC for cancer and AIDS patients by increasing appetite and decreasing nausea, blocking the spread of some cancer-causing **herpes simplex** viruses. It has been shown to assist some glaucoma patients by reducing pressure within the eye, and is used, in the form of cannabis, by a number of multiple sclerosis patients for relieving spasms. Effects include relaxation; euphoria; altered space-time perception; enhancement of visual, auditory, and olfactory senses; disorientation; and appetite stimulation. Synthetic THC, also known under the substance name *dronabinol*, is available as a prescription drug under the trade name Marinol in several countries including the United States, Netherlands, and Germany.

Description

The issue of medical uses of THC is politicized in the United States because of its status as a Schedule I drug under the U.S. Controlled Substances Act of 1970. Schedule I drugs are defined as those considered to have high potential for abuse, with no recognized medical use in treatment in the United States. In this drug's case, its recreational use is distinguished from its medical use. Marijuana is Schedule I, but tetrahydrocannabinol (THC, Marinol) is Schedule II.

There have been major advances in THC pharmacology and in understanding of the cancer disease process. In particular, research has demonstrated the

presence of numerous cannabinoid (chemical constituents of marijuana) receptors in the nucleus of the solitary tract, a brain center that is important in the control of vomiting. While other anti-vomiting drugs are equally or more effective than oral THC, Marinol, or smoked cannabis, for certain individuals unresponsive to conventional anti-emetic drugs, the use of smoked cannabis can provide relief more effectively than oral preparations which may be difficult to swallow or be expelled in vomit before having a chance to take effect. The euphoria effect of THC or smoked cannabis improves mood, whereas several conventional tranquilizers, also used in the treatment of psychoses such as schizophrenia, may produce unwanted side effects such as excessive sedation, flattening of mood, and distressing physical symptoms such as uncontrolled or compulsive movements.

There would appear to be growing evidence of direct anti-tumor activity of cannabinoids, specifically CB1 and CB2 agonists, in a range of cancer types, including brain (gliomas), skin, pituitary, prostate, and bowel. The anti-tumor activity has led in laboratory animals and in-vitro human tissues to regression of tumors, reductions in vascularisation (blood supply) and metastases (secondary tumors), as well as direct inducement of death among cancer cells. Indeed, the complex interactions of cannabinoids and receptors contribute to scientific understanding of the mechanisms by which cancers develop. However, smoking of cannabis releases a number of non-cannabinoid carcinogens into the lungs and upper respiratory tract, and a number of researchers have identified pre-cancerous changes in lung cells. The failure of these researchers to discover significant evidence of actual cancer cells in the lung may be attributed to these anti-cancer activities of cannabinoids, including THC, counteracting the effects of other carcinogens in smoked cannabis. Some researchers have investigated the link between mental and spiritual state and cancer remission, associating the cannabinoid system with the expression of pleasure on the one hand and stress on the other.

Recommended dosage

The average dose of Marinol is 5–20 mg daily. Most patients respond to 5 mg three or four times daily. Dosage may be escalated during a **chemotherapy** cycle or at subsequent cycles, based upon initial results. Therapy should be initiated at the lowest recommended dosage and increased based on clinical response. Marinol is a small soft gel and is available in three strengths: 2.5, 5, and 10 mg. The pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults. Caution is recommended in prescribing Marinol for children because of the psychoactive effects.

KEY TERMS

Cannabinoid—Chemical constituents of marijuana, such as THC.

Carcinogens—Cancer-causing agents.

Chemotherapy—The use of chemical agents to treat diseases, especially cancer.

Glaucoma—An eye disorder marked by abnormally high pressure within the eyeball.

Herpes simplex—Either of two viral diseases marked by clusters of small watery blisters, one affecting the area of the mouth and lips and the other the genitals.

Multiple sclerosis—A serious progressive disease of the central nervous system.

Precautions

THC and Marinol should be carefully evaluated in patients with the following medical conditions because of individual variation in response and tolerance to the effects of the drugs: patients with cardiac disorders; patients with a history of **substance abuse**, including alcohol abuse or dependence; mania (a psychiatric disorder characterized by excessive physical activity, rapidly changing ideas, and impulsive behavior); **depression**; or schizophrenia. Marinol and THC should be used with caution in patients receiving sedatives, hypnotics, or other psychoactive drugs because of the potential for additive or synergistic effects on the central nervous system. Marinol should be used with caution in pregnant patients, nursing mothers, or pediatric patients because it has not been studied in these populations.

Side effects

Some negative effects are associated with constant, long-term use, including memory loss, depression, and loss of motivation. The long-term effects of THC on humans is highly disputed.

Interactions

No clinically significant drug-to-drug interactions were discovered in Marinol **clinical trials**.

Ken R. Wells

Thalidomide

Definition

Thalidomide, which is also known as Thalomid, is a drug used to fight aggressive cancers, particularly those that have metastasized, or spread.

Purpose

There are many studies, either in progress or recently completed, that suggest thalidomide can slow or stop the spread of cancer of the brain, breast, colon, and prostate, as well as **multiple myeloma** (a cancer of the bone marrow). Research studies that consider the benefit of thalidomide in treating other cancers are multiplying rapidly. The use of the drug in cancer therapy is likely to increase.

Description

Thalidomide was first introduced in 1957 primarily as a tranquilizer, a medication prescribed particularly for imparting drowsiness and sleep. Then, it was given to pregnant women to provide them with relief from morning sickness. Soon after being prescribed to pregnant women, thalidomide was linked to death or severe disabilities in newborns. Some children who had been exposed to thalidomide while in the womb (in utero) failed to develop limbs or had very short limbs. Others were born blind or deaf or with other physical problems.

The same action of thalidomide that harms babies may make it useful as a powerful cancer fighter. Thalidomide interferes with the formation of blood vessels. It is called an antiangiogenic drug because angiogenesis refers to the formation of blood vessels. Studies in 2003 reported that thalidomide may use signal repression or have immunosuppression capabilities. This means it can act on the body's natural immune responses.

Cancers that spread have a lot of blood vessels (are highly vascularized). Thus, when cancer cells are not nourished by a blood supply, they die. One way to stop the spread of cancer is to stop the formation of the blood vessels that carry nourishment to the cancer cells, and that is what thalidomide is thought to do. Researchers also are interested in other activities of thalidomide, particularly the ones that make it capable of eliminating skin eruptions, such as sores, or ulcers, in the mouths of patients with AIDS and leprosy.

Recommended dosage

Dosages being used depend on the type of cancer being attacked. For example, in one study, to treat multiple myeloma, a starting dose of 200 mg per day was increased to 800 mg per day over a two-week period.

In a **colon cancer** study, 400 mg per day of thalidomide were given in combination with the anticancer drug **irinotecan**. The dose of irinotecan was between 300 and 350 mg per day. Used in combination with irinotecan, thalidomide contributed its own cancer-fighting properties and it also seemed to reduce the side effects of irinotecan.

In a trial using thalidomide to treat **prostate cancer**, both low doses (as low as 200 mg per day) and high doses (as high as 1200 mg per day) were tried. The patients taking high doses fared somewhat better.

KEY TERMS

Angiogenesis—The process by which tumors gain access to a blood supply, allowing tumor growth.

Fetus—Human embryo.

Kilogram—Metric measure that equals 2.2 pounds.

Milligram—One-thousandth of a gram; there are 1,000 grams in a kilogram. A gram is the metric measure that equals about 0.035 ounces.

Sedation—Process of reducing a particularly excited or agitated state.

Precautions

The serious threat thalidomide poses to fetuses cannot be overstated. No pregnant woman and no woman who has any chance of becoming pregnant should take thalidomide. (Only women who have had a hysterectomy or who are at the age of menopause and have been in a menopausal state, which is no menses, or periods, for 24 consecutive months, can be considered as having no chance of becoming pregnant.)

Patients taking thalidomide must meet strict criteria for use. Pharmacies that dispense thalidomide must have special registration.

Side effects

Besides the extreme risk thalidomide poses to fetuses, it also produces side effects in the person taking the drug. The side effects of thalidomide are much milder than many other anticancer drugs, and because the drug poses less discomfort than other cancer-fighting drugs, it is particularly attractive to oncologists, or physicians who treat cancer patients.

Among the side effects are erratic heartbeat, swelling (edema), digestive upsets of all sorts, including both constipation and **diarrhea**, pain in back and neck muscles, and skin problems.

Interactions

Barbiturates, salts, and esters used to encourage sleep, and alcohol increase the effect of thalidomide's power of sedation. They should not be taken with the drug. Food interferes with the absorption of thalidomide; it should be taken when the stomach is empty.

Resources

PERIODICALS

"Thalidomide May Have No Effect on Anti-gaI Antibody, But May Immunosuppress." *Cancer Weekly* November 18, 2003: 124.

"Thalidomide Uses Signal Repression to Halt Tumor Proliferation." *Health & Medicine Week* November 3, 2003: 591.

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Teresa G. Odle

Thioguanine

Definition

Thioguanine is an anticancer (antineoplastic) agent belonging to the class of drugs called antimetabolites. It also acts as a suppressor of the immune system. It is available only in the generic form in the United States, or under the brand name Lanvis in Canada. Other common designations for thioguanine include 6-thioguanine (6-TG) and TG.

Purpose

Thioguanine is used to treat various forms of acute and nonlymphocytic leukemias. It is usually used in combination with other **chemotherapy** drugs, such as **cyclophosphamide**, **cytarabine**, prednisone, and/or **vincristine**.

Description

Thioguanine chemically interferes with the synthesis of genetic material of cancer cells. It acts as a false building block for DNA and RNA, which, when used to copy DNA and RNA, leads to cell death.

Recommended dosage

Thioguanine is administered orally. It is generally given once per day in a dosage of 2 mg per kg (2.2 pounds) of body weight. This dosage may be increased to 3 mg per kg if the patient does not respond to the medication within three weeks.

Precautions

Thioguanine can cause an allergic reaction in some people. Patients with a prior allergic reaction to thioguanine or **mercaptopurine** should not take thioguanine.

Thioguanine can cause serious birth defects if either the man or the woman is taking this drug at the time of conception or if the woman is taking this drug during pregnancy. Because thioguanine is easily passed from mother to child through breast milk, breast feeding is not recommended while thioguanine is being taken.

This drug suppresses the immune system and interferes with the normal functioning of certain organs and tissues. For these reasons, it is important that the prescribing physician is aware of any of the following pre-existing medical conditions:

- a current case of, or recent exposure to, chicken pox
- herpes zoster (shingles)
- a current case, or history of, gout or kidney stones
- all current infections
- kidney disease
- liver disease

Also, because thioguanine is such a potent immunosuppressant, patients receiving this drug must exercise extreme caution to avoid contracting any new infections, and should make an effort to:

- avoid any individual with any type of infection
- avoid bleeding injuries, including those caused by brushing or flossing the teeth
- avoid contact of the hands with the eyes or nasal passages
- avoid contact sports or any other activity that could cause a bruising or bleeding injury

Side effects

A common side effect of thioguanine use is **myelosuppression** with decreases in white blood cell and platelet counts. Other possible side effects include:

- increased susceptibility to infection
- nausea and vomiting

KEY TERMS

Antineoplastic—A drug that prevents the growth of a neoplasm by interfering with the maturation or proliferation of the cells of the neoplasm.

Neoplasm—New abnormal growth of tissue.

- diarrhea
- mouth sores
- skin rash, **itching**, or hives
- swelling in the feet or lower legs

A doctor should be consulted immediately if the patient experiences:

- black, tarry or bloody stools
- blood in the urine
- persistent cough
- fever and chills
- pain in the lower back or sides
- painful or difficult urination
- unusual bleeding or bruising

Interactions

Thioguanine should not be taken in combination with any prescription drug, over-the-counter drug, or herbal remedy without prior consultation with a physician. It is particularly important that the prescribing physician be aware of the use of any of the following drugs:

- antithyroid agents
- azathioprine
- chloramphenicol
- colchicine
- flucytosine
- interferon
- plicamycin
- probenecid
- sulfinpyrazone
- zidovudine
- any **radiation therapy** or chemotherapy medicines

See also Cancer genetics; Chemoprevention; DNA flow cytometry; Drug resistance.

Paul A. Johnson, Ed.M.

Thiotepa

Definition

Thiotepa is a **chemotherapy** drug used to reduce the size of a cancerous tumor and prevent the growth of new cancer cells. This drug is sometimes referred by the brand name Thioplex.

Purpose

Thiotepa has been used in the treatment of many types of tumors, but it is most often used as a treatment for the advanced stages of **breast cancer**, **ovarian cancer**, the middle and late stages of **bladder cancer**, and to control body cavity effusions, such as **pleural effusion** and **pericardial effusion**, that occur with some cancers. It is also sometimes used for the treatment of **Hodgkin's disease** and other lymph system cancers.

Description

Thiotepa was developed in the 1950s. It has been an approved cancer drug in the United States for over 20 years.

This drug is included in the cancer drug category termed **antineoplastic agents**, which slow or prevent the growth of cancerous tumors. Specifically, thiotepa is among a group of antineoplastic agents that were designed to alter the structure of the DNA in cells, causing a cell to die or to fail to replicate itself. These drugs do not distinguish between normal and cancerous cells and thus affect both equally.

Thiotepa is among several chemotherapy drugs being investigated for use in experimental high-dose chemotherapy, where a cancer patient is given a combination of several chemotherapy drugs at higher than normal dose levels. This treatment approach has been the focus of numerous **clinical trials**, most commonly for advanced breast cancer. One high-dose breast cancer chemotherapy treatment uses a combination of thiotepa, **cyclophosphamide**, and **carboplatin**. However, based on results from studies dating from 1999 to 2000, the effect of high-dose chemotherapy treatments, including those using thiotepa, have not conclusively improved the outcome or quality of life for breast cancer patients.

One approved chemotherapy treatment for advanced stages of breast cancer, where patients have not responded to other chemotherapy treatments or have experienced a relapse after a chemotherapy treatment, is a combination drug therapy of thiotepa, **doxorubicin**, and **vinblastine**. However, the results of this and other treatment options for late-stage breast cancer are not good. Treatment with a combination of chemotherapy

drugs results in approximately 10% to 20% of patients showing no signs of cancer, and the duration of this response is usually less than 12 months.

Thiopeta is about as equally effective as the other chemotherapy drugs recommended for treating bladder cancer, including **mitomycin-C**, doxorubicin, ethoglucid, or **epirubicin**. Research results suggest that these drugs may reduce the chance for cancer recurrence but has little effect on reducing the **metastasis** of the disease. After surgical removal of a tumor, thiotepa has been shown to reduce the size of the remaining tumor in 29% of bladder cancer patients.

Body cavity effusions are a known complication for the advanced stages of many cancers, including lung cancer and breast cancer. Fluid in the heart cavity, or pericardial effusion, can be managed with the use of a procedure called a **pericardiocentesis** and the injection of thiotepa into the cavity. This treatment has been shown to result in the absence of pericardial effusion in approximately 70% to 90% of all cancer patients for at least 30 days. In a 1998 study of 23 cancer patients with pericardial effusion, 83% responded to this treatment, and the condition did not worsen for about nine months.

Recommended dosage

Patients are usually given thiotepa intravenously (directly into the vein) either as a rapid injection or through an intravenous (IV) infusion (drip). It can also be administered as an injection into a muscle or into the fluid that surrounds the spinal cord. For the treatment of body cavity effusions, it is injected through a tube into the site where this condition occurs. In bladder cancer patients, it is instilled directly into the bladder.

Each dosage is calculated based on a patient's weight at the start of each treatment. The correct dosage is carefully matched and adjusted to an individual's overall condition and response to the treatment. There is a range of doses for each method used to administer the drug, and the initial dose is usually the higher value in the range. How well the patient tolerates the treatment and the effectiveness of the dosage in treating the cancer will determine the final dosage on which the patient is maintained for the duration of the therapy.

When given intravenously, such as for breast or ovarian cancer, the initial dose is 0.4 milligram per kilogram (mg/kg) of body weight. Once the best dose for an individual patient is determined, it is given every one to four weeks.

For bladder cancer patients, an initial treatment of 60 mg of thiotepa that has been dissolved in 60 milliliters (ml) of sodium chloride is instilled directly into the bladder. If a patient has difficulty retaining this volume for two hours, the dose is reduced to 30 ml. The typical treatment cycle is once a week over a four-week period.

The dosage of thiotepa for the treatment of effusion ranges from 0.6 to 0.8 mg/kg. The dosage and duration of treatment varies with the specific site of the condition, and can be as frequent as one to two times per week.

Because **myelosuppression** is a common reaction to this drug treatment, white blood cell and platelet counts are carefully monitored, usually weekly during the treatment and for three weeks after. This condition may limit the dose level that a patient can tolerate. If blood counts are below a certain level, treatment is either postponed or the dosage is decreased in the next treatment cycle.

Precautions

As with many chemotherapy drugs, **vaccines** should not be given to patients taking thiotepa, and patients should avoid contact with people who have recently taken the oral polio vaccine. Myelosuppression can increase the chance for infection and bleeding. Contact with people who have an infection should be avoided. To decrease the chance for bleeding, aspirin or aspirin-containing medicines should not be taken. High doses of thiotepa can lead to severe cases of myelosuppression and may increase a patient's chance for a later occurrence of leukemia.

Side effects

Myelosuppression, usually **neutropenia** (decrease of the infection-fighting white cells) or **thrombocytopenia** (decrease of the platelets responsible for blood clotting), is common and usually occurs one to three weeks after each treatment, but may last throughout the therapy. **Nausea and vomiting** are uncommon and are most likely to occur six to twelve hours after the drug is given. Dizziness or a mild headache can occur within the first few hours after a treatment. **Anorexia**, **stomatitis**, **diarrhea**, infertility, **fever**, and **alopecia** are uncommon. Severe myelosuppression, stomatitis, **memory change**, and problems with thinking or speaking may result from high dose treatments. Side effects for bladder cancer treatment can include pain when urinating, blood in the urine, or inflammation of the bladder.

Coping with side effects may require making some life-style changes or in some cases, such as nausea, taking medication. Treatment options for side effects should be discussed with a doctor.

According to reports, Thiotepa conditioning regimen in patients with advanced hematologic neoplasms is associated with renal and hepatic toxicity. Relapse of hematologic malignancies after allogeneic stem cell

KEY TERMS

DNA (Deoxyribonucleic acid)—The genetic material found in each cell in the body that plays an important role in controlling many of the cell's functions. When a cell divides to create two new cells, an identical copy of its DNA is found in each. If there is an error in a cell's DNA, division may not occur.

Effusion—The collection of fluid in a body cavity or tissue due to the rupture of a blood or other body vessel, resulting from type of trauma, cancer, or other condition.

Lymph system—This system is involved in preventing bacteria and other infection-causing particles from entering into the bloodstream. It is made up of small organs called lymph nodes, which make and store infection-fighting cells, and thin tubes, or vessels, that branch into all parts of the body.

Myelosuppression— The suppression of bone marrow activity, resulting in reduction in the number of platelets, red cells, and white cells found in the circulation.

transplantation remains a common problem, in particular for patients who have advanced disease at the time of transplantation. Researchers concluded that this regimen requires modification to reduce toxicity.

Interactions

Thiotepa combined with nitrogen mustard chemotherapy drugs such as cyclophosphamide or combined with **radiation therapy** does not improve the response to this treatment and can intensify some side effects, such as myelosuppression and infertility.

See also Cancer genetics; Chemoprevention; DNA cytometry; Drug resistance.

Monica McGee, M.S.

Thoracentesis

Definition

Also known as pleural fluid analysis, thoracentesis is a procedure that removes an abnormal accumulation of fluid or air from the chest through a needle or tube.

Purpose

Thoracentesis can be performed as a diagnostic or treatment procedure. For diagnosis, only a small amount of fluid is removed for analysis. For treatment, larger amounts of air or fluid are removed to relieve symptoms.

The lungs are lined on the outside with two thin layers of tissue called pleura. The space between these two layers is called the pleural space. Normally, there is only a small amount of lubricating fluid in this space. Liquid and/or air accumulates in this space between the lungs and the ribs from many conditions. The liquid is called a **pleural effusion**; the air is called a pneumothorax. Most pleural effusions are complications emanating from metastatic malignancy, or the movement of cancer cells from one part of the body to another; these are known as malignant pleural effusions. Other causes include trauma, infection, congestive heart failure, liver disease, and renal disease. Most malignant pleural effusions are detected and controlled by thoracentesis.

Symptoms of a pleural effusion include shortness of breath, chest pain, **fever**, **weight loss**, cough, and edema. Removal of air is often an emergency procedure to prevent suffocation from pressure on the lungs. Negative air pressure within the chest cavity allows normal respiration. The accumulation of air or fluid within the pleural space can eliminate these normal conditions and disrupt breathing and the movement of air within the chest cavity. Fluid removal is performed to reduce the pressure in the pleural space and to analyze the liquid.

Thoracentesis often provides immediate abatement of symptoms. However, fluid often begins to re-accumulate. A majority of patients will ultimately require additional therapy beyond a simple thoracentesis procedure.

Precautions

Thoracentesis should never be performed by inserting the needle through an area with an infection. An alternative site needs to be found in these cases. Before undergoing this procedure, a patient must make their doctor aware of any allergies, bleeding problems or use of anticoagulants, pregnancy, or possibility of pregnancy.

Description

Prior to thoracentesis, the location of the fluid is pinpointed through **x ray**, **computed tomography** (CT) scan, or ultrasound. Ultrasound and CT are more accurate methods when the effusion is small or walled off in a pocket (loculated). A sedative may be administered in some cases but is generally not recommended. Oxygen may be given to the patient.

KEY TERMS

Axilla—Armpit.

Catheter—A tube that is moved through the body for removing or injecting fluids into body cavities.

Hypovolemic shock—Shock caused by a lack of circulating blood.

Osmotic pressure—The pressure in a liquid exerted by chemicals dissolved in it. It forces a balancing of water in proportion to the amount of dissolved chemicals in two compartments separated by a semi-permeable membrane.

Pleura—Two thin layers lining the lungs on the outside.

QUESTIONS TO ASK THE DOCTOR

- How will thoracentesis benefit me?
- Will I have to have this procedure more than once?
- How soon after this procedure can I resume my normal activities?
- Will this procedure cure my problem?
- Will I require hospitalization?

The usual place to tap the chest is below the armpit (axilla) or in the back. Under sterile conditions and local anesthesia, a needle, a through-the-needle-catheter, or an over-the-needle catheter may be used to perform the procedure. Overall, the catheter techniques may be safer. Once fluid is withdrawn, it is sent to the laboratory for analysis. If the air or fluid continue to accumulate, a tube is left in place and attached to a one-way system so that it can drain without sucking air into the chest.

Preparation

Patients should check with their doctor about continuing or discontinuing the use of any medications (including over-the-counter drugs and herbal remedies). Unless otherwise instructed, patients should not eat or drink milk or alcohol for at least four hours before the procedure, but may drink clear fluids like water, pulp-free fruit juice, or tea until one hour before. Patients should not smoke for at least 24 hours prior to thoracentesis. To avoid injury to the lung, patients should not cough, breathe deeply, or move during this procedure.

Aftercare

After the tube is removed, x rays will determine if the effusion or air is reaccumulating, though some researchers and clinicians believe chest x rays do not need to be performed after routine thoracentesis.

Risks

Reaccumulation of fluid or air are possible complications, as are hypovolemic shock (shock caused by a lack of circulating blood) and infection. Patients are at increased risk for poor outcomes if they have a recent history of anticoagulant use, have very small effusions, have significant amounts of fluid, have poor health leading into this condition, have positive airway pressure, or have adhesions in the pleural space. A pneumothorax can sometimes be caused by the thoracentesis procedure. The use of ultrasound to guide the procedure can reduce the risk of pneumothorax.

Thoracentesis can also result in hemothorax, or bleeding within the thorax. In addition, internal structures, such as the lung, diaphragm, spleen, or liver, can be damaged by needle insertion. Repeat thoracenteses can increase the risk of developing hypoproteinemia (a decrease in the amount of protein in the blood).

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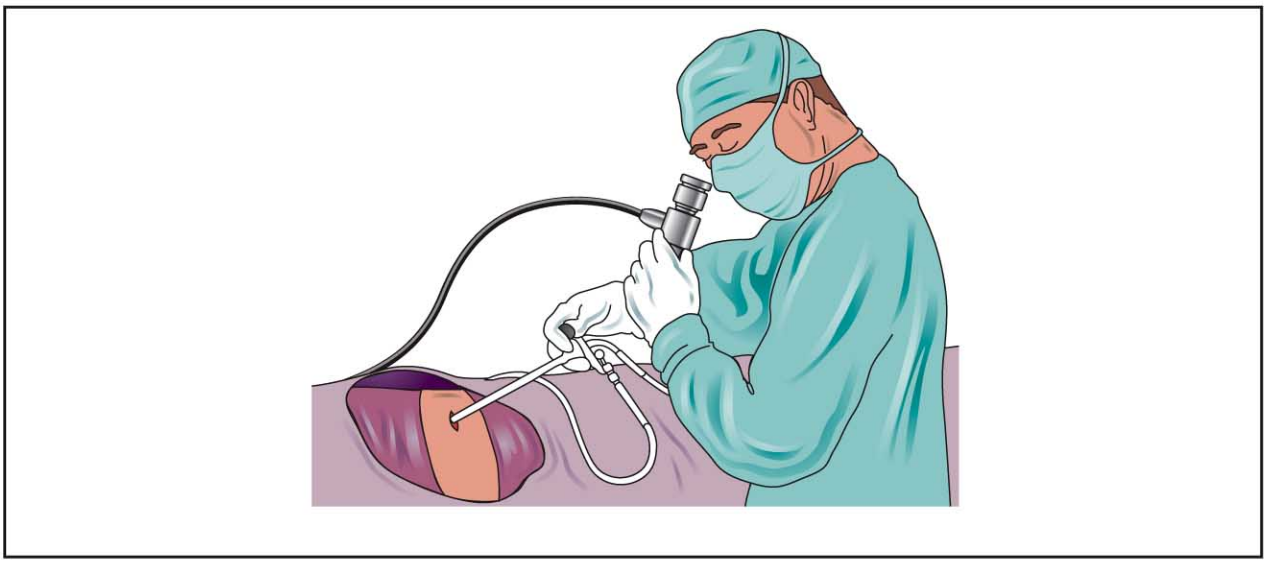
Thoracoscopy

Definition

Thoracoscopy is the insertion of an endoscope, a narrow diameter tube with a viewing mirror or camera



Thoracoscopy is a procedure in which a physician can view the chest cavity and the lungs by inserting an endoscope through the chest wall. Thoracoscopy is less invasive than surgical lung biopsy. *(Illustration by Electronic Illustrators Group.)*

attachment, through a very small incision (cut) in the chest wall.

Purpose

Thoracoscopy makes it possible for a physician to examine the lungs or other structures in the chest cavity, without making a large incision. It is an alternative to **thoracotomy** (opening the chest cavity with a large incision). Many surgical procedures, especially taking tissue samples (biopsies), can also be accomplished with thoracoscopy. The procedure is done to:

- assess lung cancer
- take a **biopsy** for study
- determine the cause of fluid in the chest cavity
- introduce medications or other treatments directly into the lungs
- treat accumulated fluid, pus (empyema), or blood in the space around the lungs

For many patients, thoracoscopy replaces thoracotomy. It avoids many of the complications of open chest surgery and reduces pain, hospital stay, and recovery time.

Precautions

Because one lung is partially deflated during thoracoscopy, the procedure cannot be done on patients whose lung function is so poor that they do not receive enough oxygen with only one lung. Patients who have had previous surgery that involved the chest cavity, or who have blood-clotting problems, are not good candidates for this procedure.

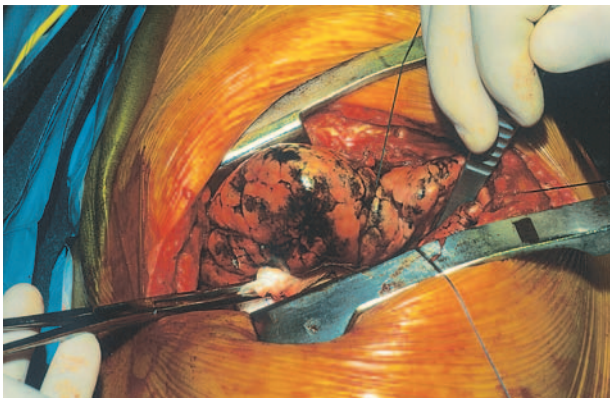
Thoracoscopy gives physicians a good but limited view of the organs, such as lungs, in the chest cavity. Endoscope technology is being refined every day, as is what physicians can accomplish by inserting scopes and instruments through several small incisions instead of making one large cut.

Description

Thoracoscopy is most commonly performed in a hospital, and general anesthesia is used. Some of the procedures are moving toward outpatient services and local anesthesia. More specific names are sometimes applied to the procedure, depending on what the target site of the effort is. For example, if a physician intends to examine the lungs, the procedure is often called pleuroscopy. The procedure takes two–four hours.

The surgeon makes two or three small incisions in the chest wall, often between the ribs. By making the incisions between the ribs, the surgeon minimizes damage to muscle and nerves and the ribs themselves. A tube is inserted in the trachea and connected to a ventilator, which is a mechanical device that assists the patient with inhaling and exhaling.

The most common reason for a thoracoscopy is to examine a lung that has a tumor or a metastatic growth of cancer. The lung to be examined is deflated to create a space between the chest wall and the lung. The patient



Thoracotomy for left upper lobectomy. The cancer is visible just above the sponge stick. *(Custom Medical Stock Photo. Reproduced by permission.)*

breathes with the other lung with the assistance of the ventilator.

A specialized endoscope, or narrow diameter tube, with a video camera or mirrored attachment, is inserted through the chest wall. Instruments for taking necessary tissue samples are inserted through other small incisions. After tissue samples are taken, the lung is re-inflated. All incisions, except one, are closed. The remaining open incision is used to insert a drainage tube. The tissue samples are sent to a laboratory for evaluation.

Preparation

Prior to thoracoscopy, the patient will have several routine tests, such as blood, urine and chest **x ray**. Older patients must have an electrocardiogram (a trace of the heart activity) because the anesthesia and the lung deflation put a big load on the heart muscle. The patient should not eat or drink from midnight the night before the thoracoscopy. The anesthesia used can cause vomiting, and, because anesthesia also causes the loss of the gag reflex, a person who vomits is in danger of moving food into the lungs, which can cause serious complications and death.

KEY TERMS

Endoscope—Instrument designed to allow direct visual inspection of body cavities, a sort of microscope in a long access tube.

Thoracotomy—Open chest surgery.

Trachea—Tube of cartilage that carries air into and out of the lungs.

QUESTIONS TO ASK THE DOCTOR

- How soon will you know the results?
- When can I resume any medications that were stopped?
- When can I resume normal activities?
- What future care will I need?

Aftercare

After the procedure, a chest tube will remain in one of the incisions for several days to drain fluid and release residual air from the chest cavity. Hospital stays range from two–five days. Medications for pain are given as needed. After returning home, patients should do only light lifting for several weeks.

Risks

The main risks of thoracoscopy are those associated with the administration of general anesthesia. Sometimes excessive bleeding, or hemorrhage, occurs, necessitating a thoracotomy to stop it. Another risk comes when the drainage tube is removed, and the patient is vulnerable to lung collapse (pneumothorax).

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Tish Davidson, A.M.

Thoracotomy

Definition

Thoracotomy is the process of making of an incision (cut) into the chest wall.

Purpose

A physician gains access to the chest cavity by cutting through the chest wall. Reasons for the entry are var-

KEY TERMS

Aorta—The major artery that carries blood away from the heart.

Catheter—A tube inserted into a body cavity to drain fluid. An example would be a urinary catheter used to drain urine from the urethra.

Diaphragm—The large flat muscle that runs horizontally across the bottom of the chest cavity.

Esophagus—The muscular tube that connects the mouth and the stomach.

Trachea—The tube made of cartilage that carries air from the nose and mouth to the lungs.

Urethra—The tube that carries urine from the bladder to the outside of the body.

QUESTIONS TO ASK THE DOCTOR

- If a biopsy is the only reason for the procedure, are thoracoscopy or a guided needle biopsy options (instead of thoracotomy)?

ied. Thoracotomy allows for study of the condition of the lungs, or removal of a lung or part of a lung, removal of a rib, and examination, treatment or removal of any organs in the chest cavity. Thoracotomy also gives access to the heart, esophagus, diaphragm and the portion of the aorta that passes through the chest cavity (thorax).

Lung cancer is the most common cancer for which a thoracotomy is necessary. Tumors and metastatic growths can be removed through the incision. A **biopsy**, or tissue sample for study, can also be taken through the incision.

Precautions

Patients must tell their physicians about all known allergies so that the safest anesthetics can be selected for the surgery. Older patients must be evaluated for heart ailments (usually with an electrocardiogram) before surgery because the anesthesia, as well as the thoracotomy, put an additional strain on the heart.

Description

The chest cavity can be entered from the side (laterally) or the front (also known as anterior or sternal aspect) or the back (also known as posterior aspect). The exact place in which the cut is made depends on why the surgery is being done. In some cases, the physician is able to make the incision between ribs (called an intercostal approach) to minimize the cuts through bone, nerves and muscle.

The incision is quite long, about seven inches. During the surgery, a tube is passed through the trachea. It usually has a branch to each lung. One lung is deflated so that it can be examined or surgery performed on it. The other lung remains expanded, and the patient breathes with the assistance of a mechanical device (a ventilator).

The pressure differences that are set up in the thoracic cavity by the movement of the diaphragm (the large muscle at the base of the thorax) make it possible for the lungs to expand and contract. The phases of expansion and contraction move air in and out of the lungs. If the pressure in the chest cavity changes abruptly, the lungs can collapse. Any fluid that collects in the cavity puts a patient at risk for infection and for reduced lung function, even collapse (pneumothorax). Thus, any entry to the chest usually requires that a chest tube remain for several days after the incision is closed.

Preparation

Patients are told not to eat after midnight the night before, or at least 12 hours before surgery. The advice is important because vomiting during surgery can cause serious complications and death. For surgery in which a general anesthetic is used, the gag reflex is often lost for several hours or longer, making it much more likely that food will enter the lungs if vomiting occurs.

Aftercare

Opening the chest cavity means cutting through muscle, nerves and often, ribs. It is a major procedure. Consequently, it most often involves a hospital stay as long as five to seven days. The skin around the drainage tube to the thoracic cavity must be kept clean and the tube must be kept unblocked.

The first two days after surgery may be spent in the intensive care unit of the hospital. A variety of tubes, catheters and monitors may be required after surgery.

Risks

The rich supply of blood vessels to the lungs makes hemorrhage, or uncontrolled bleeding, a risk. General anesthesia is required in most cases, and carries a risk, particularly unanticipated allergic reaction. After a thoracotomy, there may be drainage from the incision. There

is also the risk of infection. The patient must learn how to keep the incision clean and dry as it heals.

After a chest tube is removed, a patient is vulnerable to lung collapse (pneumothorax). Physicians aim to reduce the risk of collapse by timing the removal the tube. Doing so at the end of inspiration (breathing in) or the end of expiration (breathing out) poses less risk. Deep breathing and coughing should be emphasized as an important way patients can help themselves and prevent **pneumonia**.

See also Thoracoscopy; CT-guided biopsy.

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Diane M. Calabrese

Thrombocytopenia

Description

Thrombocytopenia (thrombocythemia) is a blood disorder characterized by an abnormally low number of circulating platelets (thrombocytes) in the bloodstream. Because platelets play an important role in the process of coagulation (blood clotting) and in the plugging of damaged blood vessels, persons with decreased platelets bruise easily and can have episodes of excessive bleeding (hemorrhage). Thrombocytopenia is usually an acquired disorder, but it can also be congenital, as in neonatal rubella (German measles).

Platelets are irregular, disc-shaped fragments of large cells called megakaryocytes, which are found in the spongy center of long bones (bone marrow). They are the smallest cell-like structures in the blood. When a blood vessel is punctured or damaged, normal mature platelets have a tendency to aggregate (group) together at the site, forming a plug that stops the bleeding. The lifespan of platelets in the blood is relatively short (five to ten days), so the bone marrow of healthy individuals is continually producing new platelets to replace the old ones.

Doctors usually use a combination of the physical examination, the medical history, and laboratory testing to diagnose this disorder. The platelet count, which is part of a complete blood count (CBC), is a key diagnostic tool. It measures the number of platelets in a volume of blood. The blood normally contains between 150,000 and 400,000 platelets per microliter (cubic millimeter or mm^3) of blood. (A million microliters is equal to one liter, or about 1.1 quarts.) In adults, a platelet count of less than 100,000/microliter is considered low, but might occur without symptoms. Abnormal bleeding often occurs when the platelet count is below 30,000/microliter. If the count falls below 10,000/microliter, abnormal external bleeding is usually evident, and serious internal bleeding can be life threatening.

Causes

Thrombocytopenia occurs when any of the following abnormal conditions exist:

- decreased production of platelets by the bone marrow
- increased destruction of circulating platelets
- increased trapping of platelets by the spleen
- platelet loss from hemorrhage

The most common cause of thrombocytopenia is a decrease in the production of platelets by the bone marrow. When abnormalities develop in the bone marrow, the megakaryocytes (platelet precursors) can lose their ability to produce platelets in sufficient amounts. This is a common side effect of blood cancers such as leukemia, which causes an abnormal growth of white blood cells in the bone marrow. These abnormal cells crowd out the normal bone marrow cells, including the platelets. Other diseases that cause this condition are tumors that spread (metastasize) to the bone, aplastic **anemia**, and viral infections such as rubella. Radiation and drugs used in cancer **chemotherapy** and in the treatment of other serious diseases can also cause the bone marrow to malfunction in this way, especially if they are used together. Some drugs, such as aspirin or **heparin**, do not actually cause a decrease in the number of platelets, but they destroy the functional ability of the platelets to aggregate.

Platelets can break down in unusually high amounts in persons with abnormalities in their blood vessel walls, with blood clots, or with man-made replacement heart valves. Devices (stents) placed inside blood vessels to keep them from closing (because of weakened walls or fat build-up) can also cause an increased destruction of platelets. In addition, severe microbial infections, infection with the human immunodeficiency virus (HIV), the virus that causes AIDS, and other changes in the immune system can speed up the removal of platelets from the circulation.

Normally, the spleen holds about one-third of the body's platelets as part of this organ's function to recycle certain aging or damaged blood cells. When liver disease or cancer of the spleen is present, the spleen can become enlarged (a condition called splenomegaly) and trap

KEY TERMS

Asymptomatic—Without symptoms.

Congenital—Existing at birth.

Gamma globulin—One of a group of proteins found in the blood that is involved in helping the body to fight infections.

Microliter—Same as a cubic millimeter. One million microliters = 1 liter = about 1.06 quarts.

Neonatal—Relating to a newborn child.

Stent—A man-made surgical device, usually tube-shaped, that is placed into a blood vessel to keep it from closing.

Transfusion—The transfer of blood from one person to another. Transfusions can be direct, in which blood is transferred from the donor to the recipient; or indirect, in which the blood is taken from the donor, stored in a container, and then given to the recipient.

many more platelets than normal. Because a greater number of platelets remain in the enlarged organ, fewer platelets are circulating in the bloodstream.

Treatments

Sometimes this disorder is asymptomatic and does not require any treatment. This is often the case when thrombocytopenia occurs in children following a viral infection. Even when the disorder is a side effect of both **radiation therapy** and chemotherapy, if the thrombocytopenia is not severe, it is often reversible on its own once the therapies end.

Treatments, when necessary, vary with the severity of the disorder, the abnormal condition that caused the disorder, and any underlying or secondary cause. When possible, the best form of treatment is to eliminate whatever is causing the condition. For example, if a drug is causing the thrombocytopenia, eliminating that drug would be the ideal solution. However, when the disorder is a side effect of chemotherapy, the patient might need to continue the drug therapy. In such cases, the doctor must decide whether it is in the best interest of the patient to continue with the same dosage, to lower the dosage, to try an alternative drug, or to give the patient a platelet transfusion. For diseases other than blood cancers, doctors can sometimes continue the chemotherapy at full dosage by also giving the patient a platelet growth factor called **Oprelvekin** (marketed as Neumega) to boost the production of normal platelets in the bone marrow.

If a dysfunctional immune system is destroying the patient's platelets, the doctor might use a corticosteroid (such as prednisone) or gamma globulin to suppress the patient's **immune response** and to help maintain adequate platelet levels. **Corticosteroids** can also have unwanted side effects, so doctors usually do not use this treatment for very long.

If an enlarged spleen is the underlying cause of the thrombocytopenia, the doctor might want to try corticosteroids or epinephrine to release platelets from the spleen. If these methods fail, surgical removal of the spleen (**splenectomy**) can help to raise the platelet level since the spleen is no longer there to capture the platelets. However, the disease that caused the enlarged spleen, such as **lymphoma** or cancer that spread to the spleen from another area of the body, should be treated as well.

If the patient is having severe external or internal bleeding as the result of injury or disease, a platelet transfusion might be necessary for immediate results. This is especially true if laboratory tests show a decreased production of platelets in the bone marrow.

Alternative and complementary therapies

A natural substance called **thrombopoietin** shows promise as a regulator of platelet production.

Many over-the-counter medicines, herbal supplements (such as garlic, ginger, feverfew, and ginko biloba) and **vitamins** can affect the ability of platelets to function properly. To determine the best treatment for a patient and to avoid drug interactions, the doctor needs to know every drug and remedy a patient is taking.

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Dominic De Bellis

Thrombopoietin

Definition

Thrombopoietin is an investigational or experimental drug that may increase the number of platelets in the bloodstream.

Purpose

Thrombopoietin is an experimental drug that may be used to treat **thrombocytopenia** (a reduced number of platelets in the blood).

Description

Thrombocytopenia, or a low number of platelets in the blood, can be a life-threatening condition. Platelets are necessary for the normal process of blood clotting. When someone experiences thrombocytopenia, a cut or bruise might not heal quickly, or at all, without medical intervention. Therefore, patients with a low platelet cell count must take special precautions, and suffer significant risk.

Thrombocytopenia is a common side effect from many common **chemotherapy** agents. These agents temporarily decrease the production of platelets, as well as white blood cells that fight infection and red blood cells that carry oxygen. **Carboplatin** is an example of an agent that has a tendency to lower platelet counts. Like other cells of the blood (white blood cells and red blood cells), the number of platelets will generally increase and return to normal over days and weeks following the administration of chemotherapy.

By reducing the severity of platelet-related side effects, thrombopoietin could allow the antitumor medication to be used at higher doses and/or for longer periods of time. Thrombopoietin may also be used in other situations in which patients have low platelet cell counts.

Thrombopoietin is derived from the gene of the same name. A laboratory-synthesized version of the human gene product encourages the development of platelet cells from precursor cells in the blood.

Thrombopoietin is an investigational, or an experimental, drug in the U.S.. This means that the FDA has not approved this drug for general use as of mid-2001. Generally, investigational drugs are made available through participation in **clinical trials**.

Recommended dosage, precautions, side effects, and interactions

As noted above, investigational drugs generally are prescribed as part of a clinical trial. Clinical trials seek to determine how effective a drug is at treating the targeted condition, the effective dose of the drug, any precautions patients should take before the drug is administered, any side effects the drug may have, and any interactions the **investigational drug** may have with other drugs. Since thrombopoietin is investigational, it is premature to discuss dosage, precautions, side effects, and interactions.

Michael Zuck, Ph.D.

KEY TERMS

Investigational drug—A drug that has not been approved for marketing by the FDA. These drugs are generally available to patients through participation in clinical trials/research studies.

Thrombocytopenia—A condition characterized by a reduced number of platelets in the blood.

Thrush

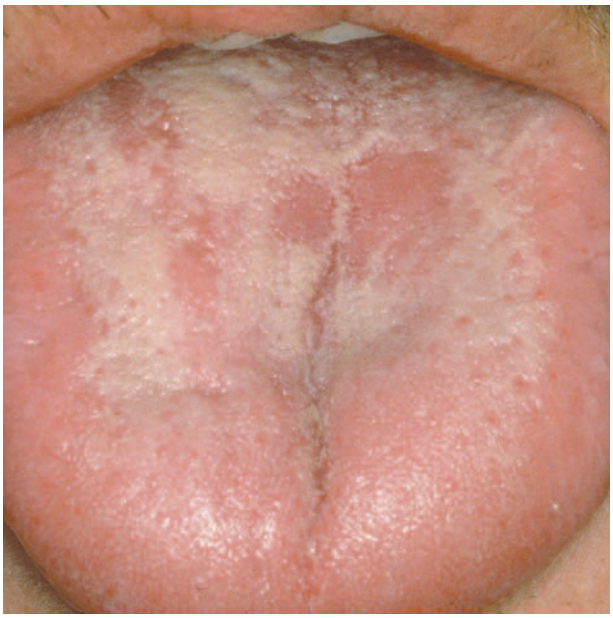
Description

Thrush (Candidiasis)is a superficial yeast infection of the mouth and throat. Other names for this common condition include oral candidiasis, oropharyngeal candidiasis, pseudomembranous candidiasis, and mycotic **stomatitis**. Thrush is characterized by the presence of thick, curd-like white patches on the tongue and inside of the cheeks. The underlying tissue is red and inflamed. The roof and floor of the mouth and the gums may also be affected. Thrush may be easily diagnosed by the appearance of the lesion. To confirm the diagnosis, a sample for microscopic analysis may be taken by scraping the lesion with a tongue depressor.

Thrush itself is a harmless infection; however, *Candida* may spread throughout the body (systemic infection) to the kidneys, lungs, joints, bones, and brain and spinal cord (central nervous system). A systemic infection can be very serious, especially in a cancer patient with a weakened immune system.

Causes

Thrush may be caused by several different species of *Candida*. Thrush rarely occurs in healthy persons. Three factors contribute to infection *Candida*: impairment of the immune system (immunosuppression), injury to the tissues (mucosa, mucous membranes) of the



This patient's tongue is infected with oral candidiasis, or thrush. *(Photograph by Edward H. Gill. Custom Medical Stock Photo. Reproduced by permission.)*

mouth, and decrease in saliva flow. In addition, thrush can occur following treatment with **antibiotics**, when normal mouth (oral) bacteria have been eliminated allowing for overgrowth of *Candida*. In addition to standard intravenous chemotherapeutic agents, **corticosteroids**, **cyclosporine** A, and interleukin-2 (aldesleukin) suppress the immune system, placing the patient at a higher risk of infection. Patients who have been treated with myeloablative therapy, as in preparation for **bone marrow transplantation**, are at a very high risk of infection. In addition, certain cancers predispose the patient to developing candidiasis, including **multiple myeloma**, **chronic lymphocytic leukemia**, **hairy cell leukemia**, **Hodgkin's disease**, and **adrenal tumors**. Malnutrition, which is not uncommon among cancer patients, also suppresses the immune system.

Patients undergoing **chemotherapy** and/or head and neck radiation are at an increased risk of developing thrush. These therapies target the rapidly dividing cancer cells.The mucosal cells which line the mouth are also rapidly dividing. The skin and mucous membranes make up the first line of defense against invading organisms and, when damaged by cancer treatments, these tissues become susceptible to infection. Chemotherapy can decrease the number of neutrophils, a type of white blood cell, causing a condition called **neutropenia**. Neutropenia significantly increases the patient's risk of infection. **Radiation therapy** reduces the number of white blood cells which impairs the immune system.

KEY TERMS

Immunosuppression—Impairment or weakening of the immune system caused by chemotherapy or radiation therapy.

Neutropenia—The condition of having low numbers of the white blood cells called neutrophils.

Oral—Pertaining to the mouth.

Systemic—Affecting the entire body.

Thrush is a temporary side effect of cancer treatment. It can take up to a year for the immune system to recover from intensive radiation therapy. Thrush that is related to the cancer may be persistent or recurrent.

Treatments

Thrush is usually treated with the antifungal drugs clotrimazole, nystatin, or amphotericin. Clotrimazole is taken as a lozenge which is allowed to dissolve slowly in the mouth. The commonly used nystatin is taken as a solution that is swished through the mouth, although recent studies have shown that nystatin may not be as effective as the newer antifungals. Amphotericin is taken as a tablet or solution. The duration of treatment may range from five to 14 days. Often, thrush resolves with local treatment alone, however, systemic medication (such as fluconazole) may be used in some cases.

The patient with thrush should faithfully conduct a daily oral hygiene routine consisting of tooth brushing two to three times, flossing once, utilizing medicated rinses as prescribed by the physician. Brushing and flossing should be performed carefully to prevent damage to the weakened oral mucosa. Dentures and other mouth appliances, which can harbor the yeast and be a source for possible reinfection, need to be disinfected.

Alternative and complementary therapies

Because there is the risk that *Candida* may spread and cause a serious systemic infection, thrush should be treated with antifungal drugs. The patient with thrush can help fight the infection by eating a well-balanced diet to counteract immunosuppression caused by malnutrition. Nutritional supplements may also be useful. Some practitioners claim that herbs (such as goldenseal or garlic) can be used to kill yeasts and boost the immune system. However, these complementary therapies should be discussed with the patient's physician because of thrush's potentially serious threat to the cancer patient.

See also Chemoprevention.

Resources

ORGANIZATIONS

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Belinda Rowland, Ph.D.

Thymic cancer

Definition

Thymic cancer refers to any one of several different types of tumors that have originated within the thymus gland.

Description

The thymus is located in the upper chest just below the neck. It is a small organ that produces certain white blood cells before birth and during childhood. These white blood cells are called lymphocytes and are an important part of the body's immune system. Once released from the thymus, lymphocytes travel to lymph nodes where they help to fight infections. The thymus gland becomes smaller in adulthood and is gradually taken over by fat tissue.

Three cell types of the thymus can give rise to cancer. The epithelial cells that make up the outer covering of the thymus can become cancerous resulting in thymic **carcinoma** and **thymoma**. When the lymphocytes in the thymus or lymph nodes become cancerous, the resulting cancers are called **Hodgkin's disease** or **non-Hodgkin's lymphomas**. A third, less common, cell type in the thymus is called Kulchitsky cells (neuroendocrine cells). These cells release chemical messengers called hormones. Cancer that originates from Kulchitsky cells is called thymic carcinoid tumors. Another type of thymic cancer, thymolipoma, is composed of thymic tissue and fatty tissue.

Although rare, thymomas are the most common type of thymic cancer. With fewer than 200 cases reported each, thymic cancer and thymic carcinoid tumors are very rare. Thymic carcinomas tend to spread more rapidly and are more aggressive than thymomas. Taken together, thymic cancers represent only about 1.5% of all malignancies.

Demographics

Thymic cancer is more common in the middle-aged and elderly; according to the National Cancer Institute (NCI), most patients diagnosed with these cancers are between 40 and 60 years of age. Thymoma and thymic carcinoma affect men and women equally. Thymic carcinoid tumors most frequently afflict men.

Causes and symptoms

The cause of thymic cancer is unknown. Cancer is caused when the normal mechanisms that control cell growth become disturbed, causing the cells to grow continually without stopping. This is caused by damage to the DNA in the cell.

Although some researchers think that previous exposure to radiation of the upper chest may be a risk factor for thymic cancer, the association has not been proved as of 2004.

Thymic tumors are not usually evident until the enlarged thymus presses on the windpipe (trachea) or blood vessels, which cause symptoms. The symptoms of thymic cancer will vary depending on what type of cancer is present. Symptoms of any thymic tumor may include: shortness of breath, swelling of the face, coughing, and chest pain.

Thymic carcinoid tumors can release hormones that may cause symptoms. Symptoms of thymic carcinoid tumors may also include red and warm skin, (flushing), **diarrhea**, and asthma.

Approximately 40% of the patients diagnosed with thymoma have no symptoms. The signs and symptoms of thymoma are vast and are related to the many disorders caused by thymoma. The most common conditions related to thymoma (**paraneoplastic syndromes**) are red cell aplasia, **myasthenia gravis**, and hypogammaglobulinemia. These conditions are autoimmune diseases, those in which the body mounts an attack against certain normal cells of the body. About 47% of thymomas are associated with myasthenia gravis. Symptoms of thymoma may also include:

- muscle weakness (especially in the eyes, neck, and chest, causing problems with vision, swallowing, and breathing)
- weakness
- dizziness

- shortness of breath
- **fatigue**

Diagnosis

The physician will conduct a complete physical examination. He or she may be able to feel a fullness in the lower neck region. Routine blood tests may be performed. **Imaging studies** are necessary because the symptoms of thymic cancer can be caused by many other diseases. Thymic tumors can be identified by chest **x ray**, **magnetic resonance imaging** (MRI), and **computed tomography** (CT). About half of these tumors can be detected by a plain-film chest x-ray.

A **biopsy** may be performed, in which a small sample of the tumor is removed and examined under the microscope. However, because of the risk of "seeding" cancerous cells, biopsies are not routinely performed. Because other tumors can lie in the region of the thymus, thymic cancer can be diagnosed only by identification of the cells that make up the tumor. There are a few different methods for biopsy of a thymic tumor. For a **mediastinoscopy**, a wand-like lighted camera (endoscope) and special instruments are passed through a small cut in the lower neck. The surgeon can see the tumor on a monitor and can cut off small samples for microscopic analysis. Mediastinoscopy is performed under general anesthesia. Alternatively, a needle biopsy will be taken in which a long needle is passed through the skin and into the tumor. Fine needle biopsy uses a thin needle and larger-core needle biopsy uses a wider needle. Needle biopsies may be performed in conjunction with computed tomography imaging.

Patients who are having difficulty breathing may have a **bronchoscopy** performed to examine the wind pipe. An endoscope, in this case a bronchoscope, is inserted through the mouth and into the windpipe. The physician will look for tumors and may perform biopsies.

Treatment team

The treatment team for thymic cancer may include a hematologist, pulmonologist, immunologist, oncologist, thoracic surgeon, cardiologist, radiation oncologist, nurse oncologist, psychiatrist, psychological counselor, and social worker.

Clinical staging, treatments, and prognosis

Clinical staging

There is more than one type of staging system for thymic cancer but the Masaoka system is used most often. This staging system was developed for thymoma, however, it is sometimes used to stage the other thymic cancers as well. Thymic carcinoma is graded (low or high) based on the cell type present in the tumor. Thymoma is categorized into four stages (I, II, III, and IV) which may be further subdivided (A and B) based on the spread of cancerous tissue. The Masaoka staging system is as follows:

- Stage I. The thymoma lies completely within the thymus.
- Stage II. The thymoma has spread out of the thymus and invaded the outer layer of the lung (pleura) or nearby fatty tissue.
- Stage III. The thymoma has spread to other neighboring tissues of the upper chest including the outer layer of the heart (pericardium), the lungs, or the heart's main blood vessels.
- Stage IVA. The thymoma has spread throughout the pericardium and/or the pleura.
- Stage IVB. The thymoma has spread to organs in other parts of the body.

Treatments

The treatment for thymic cancer depends on the type and stage of cancer and the patient's overall health. Because thymic cancers are so rare, there are no defined treatment plans. Treatment options include surgery, **radiation therapy**, and/or **chemotherapy**. Surgical removal of the tumor is the preferred treatment. Surgery is often the only treatment required for stage I thymic cancers. A treatment that is intended to aid the primary treatment is called adjuvant therapy. For instance, chemotherapy may be used along with surgery to treat thymic cancer. Stages II, III, and IV thymic cancers are often treated with surgery and some form of adjuvant therapy.

As of 2004, the preferred approach to thymic carcinoma is a combination of aggressive surgical treatment, chemotherapy using platinum-based compounds, and radiation treatments.

SURGERY Thymic cancer may be treated by resection (surgical removal) of the tumor and some of the nearby healthy tissue. Removal of the entire thymus is called a thymectomy. Surgery on the thymus is usually performed through the chest wall by splitting open the breast bone (sternum), a procedure called a median sternotomy. When complete removal of the tumor is impossible, the surgeon will remove as much of the tumor as possible (debulking surgery, subtotal resection). In these cases, If the tumor has spread, surgery may include removal of other tissues such as the pleura, pericardium, blood vessels of the heart, lung, and nerves.

RADIATION THERAPY Radiation therapy uses high-energy radiation from x rays and gamma rays to kill the cancer cells. Radiation given from a machine that is outside the body is called external radiation therapy. Radiation therapy is often used as adjuvant therapy following surgery to reduce the chance of cancer recurrence. Radiation may be used to kill cancer cells in cases in which the tumor was only partially removed. It may be used before surgery to shrink a large tumor. Radiation therapy is not very effective when used alone, although it may be used alone when the patient is too sick to withstand surgery.

The skin in the treated area may become red and dry and may take as long as a year to return to normal. Radiation to the chest may damage the lung causing shortness of breath and other breathing problems. Also, the tube that goes between the mouth and stomach (esophagus) may be irritated by radiation causing swallowing difficulties. Fatigue, upset stomach, diarrhea, and nausea are also common complaints of patients having radiation therapy. Most side effects go away about two to three weeks after radiation therapy has ended.

CHEMOTHERAPY Chemotherapy uses anticancer drugs to kill the cancer cells. The drugs are given by mouth (orally) or intravenously. They enter the bloodstream and can travel to all parts of the body. Chemotherapy may be given before surgery to shrink a tumor, which is called neoadjuvant therapy. Thymic tumor cells are very sensitive to anticancer drugs, especially **cisplatin**, **doxorubicin**, and **ifosfamide**. Generally, a combination of drugs is given because it is more effective than a single drug in treating cancer.

The side effects of chemotherapy are significant and include stomach upset, nausea and vomiting, appetite loss (anorexia), hair loss (**alopecia**), mouth sores, and fatigue. Women may experience vaginal sores, menstrual cycle changes, and premature menopause. There is also an increased chance of infections.

Prognosis

The approximate five-year survival rates are 35% for thymic carcinomas and 60% for thymic carcinoids. The five-year survival rates for thymomas are 96% for stage I, 86% for stage II, 69% for stage III, and 50% for stage IV.

Thymomas rarely spread (metastasize) but thymic carcinomas frequently spread to distant organs. Thymic carcinomas spread most often to the pleura, lung, local lymph nodes (bean-sized structures that contain lymphocytes), bone, and liver. Thymic carcinoid tumors commonly spread to local lymph nodes.

KEY TERMS

Adjuvant therapy—A treatment that is intended to aid the primary treatment. Adjuvant treatments for thymic cancer are radiation therapy and chemotherapy.

Lymphocyte—A type of white blood cell that is found in the thymus.

Neoadjuvant therapy—Radiation therapy or chemotherapy used to shrink a tumor before surgical removal of the tumor.

Paraneoplastic syndrome—A set of symptoms that is associated with cancer but is not directly caused by the cancer.

Pleura—The outer covering of the lungs.

Resection—Surgical removal of all or part of an organ or tissue.

Thymomas are prone to recurrence, even 10–15 years following surgery. For thymomas, recurrence rates are drastically reduced and the five-year survival rates are drastically increased in patients who receive adjuvant radiation therapy. Recurrence of thymic carcinoid tumors is common.

Thymomas are also associated with an increased risk of second malignancies.

Alternative and complementary therapies

Although alternative and complementary therapies are used by many cancer patients, very few controlled studies on the effectiveness of such therapies exist. Mind-body techniques such as prayer, biofeedback, visualization, meditation, and yoga, have not shown any effect in reducing cancer but they can reduce stress and lessen some of the side effects of cancer treatments. Gerson, macrobiotic, orthomolecular, and Cancell therapies are ineffective treatments for cancer.

Clinical studies of hydrazine sulfate found that it had no effect on cancer and even worsened the health and well-being of the study subjects. One clinical study of the drug amygdalin (Laetrile) found that it had no effect on cancer. Laetrile can be toxic and has caused deaths. Shark cartilage, although highly touted as an effective cancer treatment, is an improbable therapy that has not been the subject of clinical study. Although the results are mixed, clinical studies suggest that melatonin may increase the survival time and quality of life for cancer patients.

Selenium in safe doses may delay the progression of thymic cancer. Laboratory and animal studies suggest

that curcumin, the active ingredient of turmeric, has anticancer activity. Maitake mushrooms may boost the immune system, according to laboratory and animal studies. The results of laboratory studies suggest that mistletoe has anticancer properties; however, clinical studies have not been conducted.

For more comprehensive information, the reader may wish to consult the book on complementary and alternative medicine published by the American Cancer Society listed in the Resources section.

Coping with cancer treatment

The patient should consult his or her treatment team regarding any side effects or complications of treatment. Many of the side effects of chemotherapy can be relieved by medications. Patients should consult a psychotherapist and/or join a support group to deal with the emotional consequences of cancer and its treatment.

Clinical trials

As of late 2004, there were two active **clinical trials** studying thymic cancer, both sponsored by the National Cancer Institute. One trial (#E-1C99) was studying the effectiveness and toxicity of **carboplatin** and **paclitaxel** on thymic cancers. This study was open to patients with invasive, recurrent, or metastatic thymoma or thymic carcinoma. The other clinical trial was an evaluation of the effectiveness of BG00001, an investigational drug. The National Cancer Institute web site has information on these and other studies. Patients should consult with their treatment team to determine if they are candidates for these or any other ongoing studies.

Prevention

Because there are no risk factors for the development of thymic cancer known with certainty, there are no preventive measures. However, there may be an association between thymic cancer and exposure of the chest to radiation.

Special concerns

Damage to the lungs and/or esophagus caused by radiation therapy to the upper chest is a concern. Biopsy runs the risk of seeding tumor cells to other parts of the body.

Because of the increased risk of second malignancies, patients diagnosed with thymomas should have lifelong surveillance.

See also Thoracotomy.

QUESTIONS TO ASK THE DOCTOR

- What type of thymic cancer do I have?
- What stage of cancer do I have?
- Has the cancer spread?
- What is the five-year survival rate for patients with this type of cancer?
- Will you perform a biopsy?
- What type of biopsy will you perform?
- What is the risk of seeding cancerous cells during a biopsy?
- What are my treatment options?
- What are the risks and side effects of these treatments?
- What medications can I take to relieve treatment side effects?
- Are there any clinical studies underway that would be appropriate for me?
- What effective alternative or complementary treatments are available for thymic cancer?
- How debilitating is the treatment? Will I be able to continue working?
- What is the chance that the cancer will recur?
- What are the signs and symptoms of recurrence?
- What can be done to prevent recurrence?
- How often will I have follow-up examinations?

Resources

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Giaccone, Giuseppe. "Treatment of Thymoma and Thymic Carcinoma." *Annals of Oncology* 11, Supplement 3 (2000): 245–6.

ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) ACS-2345. <http://www.cancer.org>.

Cancer Research Institute, National Headquarters. 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

National Institutes of Health. National Cancer Institute. 9000 Rockville Pike, Bethesda, MD 20982. Cancer Information Service: (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

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Belinda Rowland, Ph.D.
Rebecca J. Frey, PhD

Thymoma

Definition

Thymomas are the most common tumor of the thymus.

Description

The thymus is located in the upper chest just below the neck. It is a small organ that produces certain white blood cells before birth and during childhood. These white blood cells are called lymphocytes and are an important part of the body's immune system. Once released from the thymus, lymphocytes travel to lymph nodes where they help to fight infections. The thymus gland becomes smaller in adulthood and is gradually taken over by fat tissue.

Although rare, thymomas are the most common type of thymic tumor. The term thymoma traditionally refers to a non-invasive, localized (only in the thymus) type of thymic tumor. Thymomas arise from thymic epithelial cells, which make up the covering of the thymus. Thymomas frequently contain lymphocytes, which are non-cancerous. Thymomas are classified as either noninvasive (previously called benign) or invasive (previously called malignant). Noninvasive thymomas are those in which the tumor is encapsulated and easy to remove. Invasive thymomas have spread to nearby structures (such as the lungs) and are difficult to remove. Approximately 30% to 40% of thymomas are of the invasive type.

Demographics

Thymoma affects men and women equally. It is usually diagnosed between the ages of 40 and 60 years. Thymomas are uncommon in children.

Causes and symptoms

The cause of thymoma is unknown. Cancer is caused when the normal mechanisms that control cell growth become disturbed, causing the cells to grow continually without stopping. This is caused by damage to the DNA in the cell.

Approximately 40% of the patients diagnosed with thymoma have no symptoms. The symptoms in the remaining 60% of patients are caused by pressure from the enlarged thymus on the windpipe (trachea) or blood vessels or by **paraneoplastic syndromes**. Paraneoplastic syndromes are collections of symptoms in cancer patients that cannot be explained by the tumor. Seventy-one percent of thymomas are associated with paraneoplastic syndromes. The most common syndromes related to thymoma are pure red cell aplasia (having abnormally low levels of red blood cells), **myasthenia gravis** (a muscular disorder), and hypogammaglobulinemia (having abnormally low levels of antibodies). These conditions are autoimmune diseases, those in which the body mounts an attack against certain normal cells of the body. Regarding myasthenia gravis, 15% of patients with this syndrome have thymomas. Alternately, 50% of patients with thymomas have myasthenia gravis. The relationship between the two entities is not clearly understood, though it is believed that the thymus may give incorrect instructions about the production of acetypcho-

line receptor antibodies, thus setting the state for faulty neuromuscular transmission. The confirmed presence of either thymomas or myasthenia gravis should prompt investigation for the other condition.

Symptoms of thymoma may include:

- shortness of breath
- swelling of the face
- coughing
- chest pain
- muscle weakness (especially in the eyes, neck, and chest, causing problems with vision, swallowing, and breathing)
- weakness
- dizziness
- shortness of breath
- **fatigue**

Diagnosis

The physician will conduct a complete physical exam. He or she may be able to feel a fullness in the lower neck region. Routine blood tests may be performed. **Imaging studies** are necessary because the symptoms of thymoma can be caused by many other diseases. Thymomas can be identified by chest **x ray**, **magnetic resonance imaging** (MRI), and **computed tomography** (CT).

A **biopsy** may be performed, in which a small sample of the tumor is removed and examined under the microscope. However, because of the risk of "seeding" cancerous cells, biopsies are not routinely performed. There are a few different methods to biopsy a thymoma. For a **mediastinoscopy**, a wand-like lighted camera (endoscope) and special instruments are passed through a small cut in the lower neck. The surgeon can see the tumor on a monitor and can cut off small samples for microscopic analysis. Mediastinoscopy is performed under general anesthesia. Alternatively, a needle biopsy will be taken in which a long needle is passed through the skin and into the tumor. Fine needle biopsy uses a thin needle and larger-core needle biopsy uses a wider needle. Needle biopsies may be performed in conjunction with computed tomography imaging.

Patients who are having difficulty breathing may have a **bronchoscopy** performed to examine the wind pipe. An endoscope, in this case a bronchoscope, is inserted through the mouth and into the windpipe. The physician will look for tumors and may perform biopsies.

Treatment team

The treatment team for thymoma may include a hematologist, pulmonologist, immunologist, oncologist, thoracic surgeon, cardiologist, radiation oncologist, nurse oncologist, psychiatrist, psychological counselor, and social worker.

Clinical staging, treatments, and prognosis

Clinical staging

There is more than one type of staging system for thymoma but the Masaoka system, a surgical staging system developed in 1981, is used most often. Thymoma is categorized into four stages (I, II, III, and IV) which may be further subdivided (A and B) based on the spread of cancerous tissue. The Masaoka staging system is as follows:

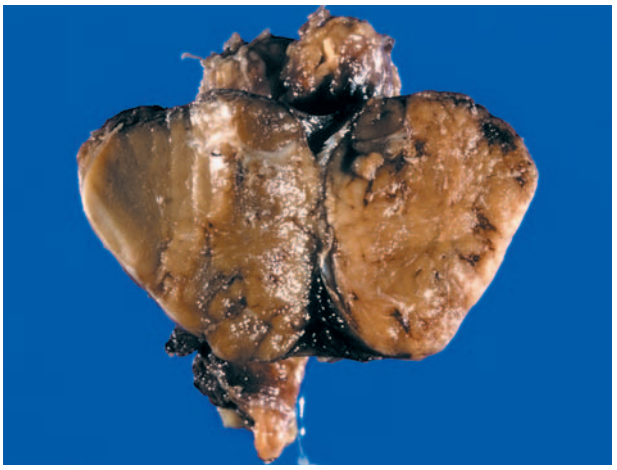
- Stage I. The thymoma lies completely within the thymus.
- Stage II. The thymoma has spread out of the thymus and invaded the outer layer of the lung (pleura) or nearby fatty tissue.
- Stage III. The thymoma has spread to other neighboring tissues of the upper chest including the outer layer of the heart (pericardium), the lungs, or the heart's main blood vessels.
- Stage IVA. The thymoma has spread throughout the pericardium and/or the pleura.
- Stage IVB. The thymoma has spread to organs in other parts of the body.

In 1999, the World Health Organization (WHO) adopted a new classification system for thymic tumors. This system is a histologic classification, which means that it is based on the microscopic features of the cells that make up the tumor. The WHO classification system ranks thymomas into types A, AB, B1, B2, B3, and C, by increasing severity.

Treatments

The treatment for thymoma cancer depends on the stage of cancer and the patient's overall health. Because thymomas are so rare, there are no defined treatment plans. Treatment options include surgery, **radiation therapy**, and/or **chemotherapy**. Surgical removal of the tumor is the preferred treatment. Surgery is often the only treatment required for stage I tumors. Treatment of thymoma often relieves the symptoms caused by paraneoplastic syndromes.

A treatment that is intended to aid the primary treatment is called adjuvant therapy. For instance, chemotherapy may be used along with surgery to treat



Gross specimen of the human thymus gland cut through showing a tumor (thymoma). *(Copyright Science Source/Photo Researchers, Inc. Reproduced by permission.)*

thymoma. Stages II, III, and IV thymomas are often treated with surgery and some form of adjuvant therapy.

SURGERY Thymoma may be treated by surgically removing (resecting) the tumor and some of the nearby healthy tissue. Removal of the entire thymus gland is called a thymectomy. Surgery on the thymus is usually performed through the chest wall by splitting open the breast bone (sternum), a procedure called a median sternotomy. When complete removal of the tumor is impossible, the surgeon will remove as much of the tumor as possible (debulking surgery, sub-total resection). In these cases, if the tumor has spread, surgery may include removal of other tissues such as the pleura, pericardium, blood vessels of the heart, lung, and nerves.

RADIATION THERAPY Radiation therapy uses high-energy radiation from x rays and gamma rays to kill the cancer cells. Radiation given from a machine that is outside the body is called external radiation therapy. Radiation therapy is often used as adjuvant therapy following surgery to reduce the chance of cancer recurrence. Radiation may be used to kill cancer cells in cases in which the tumor was only partially removed. It may be used before surgery to shrink a large tumor. Radiation therapy is not very effective when used alone, although it may be used alone when the patient is too sick to withstand surgery.

The skin in the treated area may become red and dry and may take as long as a year to return to normal. Radiation to the chest may damage the lung causing shortness of breath and other breathing problems. Also, the tube that goes between the mouth and stomach (esophagus) may be irritated by radiation causing swallowing difficulties. Fatigue, upset stomach, **diarrhea**, and nausea are also common complaints of patients having radiation therapy. Most side effects go away about two to three weeks after radiation therapy has ended.

CHEMOTHERAPY Chemotherapy uses anticancer drugs to kill the cancer cells. The drugs are given by mouth (orally) or intravenously. They enter the bloodstream and can travel to all parts of the body. Chemotherapy may be given before surgery to shrink a tumor, which is called neoadjuvant therapy. Thymoma cells are very sensitive to anticancer drugs, especially **cisplatin**, **doxorubicin**, and **ifosfamide**. Generally, a combination of drugs is given because it is more effective than a single drug in treating cancer. **Corticosteroids** are also used to treat thymoma.

The side effects of chemotherapy are significant and include stomach upset, nausea and vomiting, appetite loss (anorexia), hair loss (**alopecia**), mouth sores, and fatigue. Women may experience vaginal sores, menstrual cycle changes, and premature menopause. There is also an increased chance of infections.

Prognosis

The five-year survival rates for thymomas are 96% for stage I, 86% for stage II, 69% for stage III, and 50% for stage IV. Thorough (radical) surgery is associated with a longer survival rate. Almost 15% of thymoma patients develop a second cancer.

Thymomas rarely spread (metastasize) outside of the chest cavity. **Metastasis** is usually limited to the pleura. Invasive thymomas are prone to recurrence, even 10 to 15 years following surgery. The recurrence rates are drastically reduced and the five-year survival rates are drastically increased in patients who receive adjuvant radiation therapy.

Alternative and complementary therapies

Although alternative and complementary therapies are used by many cancer patients, very few controlled studies on the effectiveness of such therapies exist. Mind-body techniques such as prayer, biofeedback, visualization, meditation, and yoga have not shown any effect in reducing cancer but they can reduce stress and lessen some of the side effects of cancer treatments. Gerson, macrobiotic, orthomolecular, and Cancell therapies are ineffective treatments for cancer.

Clinical studies of hydrazine sulfate found that it had no effect on cancer and even worsened the health and well-being of the study subjects. One clinical study of the drug amygdalin (Laetrile) found that it had no effect on cancer. Laetrile can be toxic and has caused deaths. Shark cartilage, although highly touted as an effective cancer treatment, is an improbable therapy that has not been the

KEY TERMS

Adjuvant therapy—A treatment that is intended to aid the primary treatment. Adjuvant treatments for thymic cancer are radiation therapy and chemotherapy.

Invasive—A descriptive term for thymoma that has spread beyond the outer wall of the thymus.

Lymphocyte—A type of white blood cell that is found in the thymus.

Neoadjuvant therapy—Radiation therapy or chemotherapy used to shrink a tumor before surgical removal of the tumor.

Paraneoplastic syndrome—A set of symptoms that is associated with cancer but is not directly caused by the cancer.

Pleura—The outer covering of the lungs.

QUESTIONS TO ASK THE DOCTOR

- What histologic class of thymoma do I have?
- What stage of cancer do I have?
- Has the cancer spread?
- What is the five-year survival rate for patients with this stage of thymoma?
- Will you perform a biopsy?
- What type of biopsy will you perform?
- What is the risk of seeding during a biopsy?
- What are my treatment options?
- What are the risks and side effects of these treatments?
- What medications can I take to relieve treatment side effects?
- Are there any clinical studies underway that would be appropriate for me?
- What effective alternative or complementary treatments are available for thymoma?
- How debilitating is the treatment? Will I be able to continue working?
- What is the chance that the cancer will recur?
- What are the signs and symptoms of recurrence?
- What can be done to prevent recurrence?
- How often will I have follow-up examinations?

subject of clinical study. Although the results are mixed, clinical studies suggest that melatonin may increase the survival time and quality of life for cancer patients.

Selenium, in safe doses, may delay the progression of cancer. Laboratory and animal studies suggest that curcumin, the active ingredient of turmeric, has anticancer activity. Maitake mushrooms may boost the immune system, according to laboratory and animal studies. The results of laboratory studies suggest that mistletoe has anticancer properties; however, clinical studies have not been conducted.

For more comprehensive information, the reader should consult the book on complementary and alternative medicine published by the American Cancer Society listed in the Resources section.

Coping with cancer treatment

The patient should consult his or her treatment team regarding any side effects or complications of treatment. Many of the side effects of chemotherapy can be relieved by medications. Patients should consult a psychotherapist and/or join a support group to deal with the emotional consequences of cancer and its treatment.

Clinical trials

As of early 2001, there were two active **clinical trials** studying thymoma. The National Cancer Institute sponsored both studies. One trial (#E-1C99) was studying the effectiveness and toxicity of **carboplatin** and **paclitaxel** on thymoma. This study was open to patients with invasive, recurrent, or metastatic thymoma. The other study (#E-1C97) was studying the effectiveness and toxicity of octreotide both with and without prednisone for metastatic or recurrent thymoma. The National Cancer Institute web site has information on these and other studies. Patients should consult with their treatment team to determine if they are candidates for these or any other ongoing studies.

Prevention

Because there are no known risk factors for the development of thymoma there are no preventive measures. However, there may be an association between **thymic cancer** and exposure of the chest to radiation.

Special concerns

Damage to the lungs and/or esophagus caused by radiation therapy to the upper chest is a concern. Biopsy

runs the risk of seeding tumor cells to other parts of the body.

See also Thoracotomy.

Resources

BOOKS

Bruss, Katherine, Christina Salter, and Esmeralda Galan, editors. *American Cancer Society's Guide to Complementary and Alternative Cancer Methods*. Atlanta: American Cancer Society, 2000.

Cameron, Robert, Patrick Loehrer, and Charles Thomas. "Neoplasms of the Mediastinum." In *Cancer: Principles and Practice of Oncology*, edited by Vincent T. DeVita, Samuel Hellman, and Steven Rosenberg. Philadelphia: Lippincott Williams & Wilkins, 2001.

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Muller-Hermelink, H., and A. Marx. "Thymoma." *Current Opinion in Oncology* 12 (September 2000): 426–33.

Thomas, Charles, Cameron Wright, and Patrick Loehrer. "Thymoma: State of the Art." *Journal of Clinical Oncology* 17 (July 1999): 2280–9.

ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) ACS-2345. <http://www.cancer.org>.

Cancer Research Institute, National Headquarters. 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

National Institutes of Health. National Cancer Institute. 9000 Rockville Pike, Bethesda, MD 20982. Cancer Information Service: (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

Belinda Rowland, Ph.D.

Thyroid nuclear medicine scan *see* **Thyroid scan**

Thyroid cancer

Definition

Thyroid cancer is a disease in which the cells of the thyroid gland become abnormal, grow uncontrollably and form a mass of cells called a tumor.

Description

The thyroid is a hormone-producing, butterfly-shaped gland located in the neck at the base of the throat. It has two lobes, the left and the right. The thyroid uses iodine, a mineral found in some foods, to make several of its hormones. Thyroid hormones regulate essential body processes such as heart rate, blood pressure, body temperature, metabolism, and affect the nervous system, muscles and other organs. These hormones also play an important role in regulating childhood growth and development.

Types of thyroid cancer

Thyroid cancer is grouped into four types based on how its cells appears under a microscope. The types are papillary, follicular, medullary and anaplastic thyroid cancers. They grow at different rates and can spread to other parts of the body if left untreated.

PAPILLARY The papillary type (60%–80% of all thyroid cancers) is a slow-growing cancer that develops in the hormone-producing cells that contain iodine.

FOLLICULAR The follicular type (30%–50% of thyroid cancers) also develops in the hormone-producing cells.

MEDULLARY The medullary type (5%–7% of all thyroid cancers) develops in the parafollicular cells (also known as the C cells) that produce **calcitonin**, a hormone that does not contain iodine.

ANAPLASTIC The fourth type of thyroid cancer, anaplastic (2% of all thyroid cancers), is the fastest growing, most aggressive thyroid cancer type.

Demographics

Diseases of the thyroid gland affect millions of Americans. The most common diseases of the thyroid are either hyperthyroidism (Grave's disease) or hypothyroidism, an overactive or an underactive gland, respectively. Sometimes lumps or masses may develop in the thyroid. Although most (95%) of these lumps or nodules are noncancerous (benign), all thyroid lumps should be taken seriously. The American Cancer Society estimates that in 2001, approximately 19,500 new cases of thyroid cancer will have been diagnosed in the United States.

Women are three times more likely to develop thyroid cancer than men. Although the disease affects teenagers and young adults, most people who develop thyroid cancer are over 50 years of age. Caucasians are affected more often than African Americans.

Causes and symptoms

The exact cause of thyroid cancer is not known but some risk factors have been identified. Radiation was

used in the 1950s and 1960s to treat acne and to reduce swelling in infections of the tonsils, adenoids and lymph nodes. It has been proven that this exposure is a risk factor for thyroid cancer. In some areas of the world, diets are low in iodine. Papillary and follicular cancers occur more frequently in these areas. Iodine deficiency is not a large problem in the United States because iodine is added to table salt and other foods. Approximately 7% of thyroid cancers are caused by the alteration (mutation) of a gene called the RET oncogene, which can be inherited.

Symptoms are rare, and the lump is not usually painful. The symptoms of thyroid nodules are:

- A lump or nodule that can be felt in the neck is the most frequent sign of thyroid cancer.
- The lymph nodes may be swollen and the voice may become hoarse because the tumor presses on the nerves leading to the voice box.
- Some patients experience a tight or full feeling in the neck and have difficulty breathing or swallowing.

Diagnosis

Physicians use several tests to confirm the suspicion of thyroid cancer, to identify the size and location of the lump and to determine whether the lump is non-cancerous (benign) or cancerous (malignant).

A blood test called the thyroid stimulating hormone (TSH) test checks thyroid function. The blood is drawn by a technician with a needle and the test takes a few minutes. The results take several days to be interpreted by a pathologist.

A test known as the calcitonin test may be ordered. Calcitonin is a hormone produced by the C cells (parafollicular cells) of the thyroid gland. The hormone is produced in excess when the parafollicular cells of the thyroid become cancerous. Blood calcitonin levels are used to confirm the diagnosis of medullary thyroid cancer if it is suspected.

Computed tomography scan (CT scan) or **ultrasonography** (an ultrasound scan) are imaging tests used to produce a picture of the thyroid. A radiologist usually interprets the results of these tests within 24 hours. In ultrasonography, high-frequency sound waves are bounced off the thyroid. The pattern of echoes that is produced by these waves is converted into a computerized image on a television screen. This test can determine whether the lumps found in the thyroid are benign fluid-filled cysts or solid malignant tumors.

A radioactive scan (a thyroid nuclear medicine scan) may take several hours and can be used to identify any abnormal areas in the thyroid. For this test, the patient is given a very small amount of radioactive iodine which can either be swallowed or injected. Since the thyroid is the only gland in the body that absorbs iodine, the radioactive iodine accumulates there. An x-ray image can then be taken or an instrument called a "scanner" can be used to identify areas in the thyroid that do not absorb iodine normally. These abnormal spots are called "cold spots" and further tests are performed to check whether the cold spots are benign or malignant tumors. If a significant amount of radioactive iodine is concentrated in the nodule, then it is termed "hot" and is usually benign. Again a radiologist interprets the results within a day.

The most accurate diagnostic tool for thyroid cancer is a **biopsy**. In this process, a sample of thyroid tissue is withdrawn and examined under a microscope by a pathologist. This usually takes a day or so. The tissue samples can be obtained either by drawing out a sample of tissue through a needle (needle biopsy) or by surgical removal of the nodule (surgical biopsy). A needle biopsy takes a few minutes and can be done by any trained physician, usually a radiologist. The surgical biopsy is done by a surgeon under general anesthesia with the help of an anesthesiologist and will take a few hours. If thyroid cancer is diagnosed, further tests may be done to learn about the stage of the disease and help doctors plan appropriate treatment.

Treatment team

The types of healthcare providers often involved in the care of patients are surgeons, internal medicine specialists, pathologists, radiologists, endocrinologists, anesthesiologists, hematologist-oncologists (cancer specialists) and radiation-oncologists.

Clinical staging, treatment and prognosis

Staging

The aggressiveness of each type of thyroid cancer is different. Cancer staging considers the size of the tumor, whether it has grown into surrounding lymph nodes and whether it has spread to distant parts of the body (metastasized). Age and general health status are also taken into account. The **American Joint Commission on Cancer** (AJCC) staging is summarized below for each thyroid cancer type.

PAPILLARY AND FOLLICULAR In patients younger than 45 years:

- Stage I refers to patients without evidence of cancer beyond the thyroid.
- Stage II refers to patients with spread of cancer outside the thyroid gland.

In patients over 45:

- Stage I: Tumors are smaller than one cm (0.3 in).
- Stage II: Tumors have not broken through the capsule (covering) of the thyroid.
- Stage III: Tumors have spread locally to the nearby lymph nodes.
- Stage IV: Tumors have spread outside the thyroid area (distant metastases). In the case of Stage IV cancer, the places to which thyroid cancer often metastasizes are the lungs and bone.

MEDULLARY

- Stage I: Tumor is less than 1 cm (0.3 in) or is only detected by a provocative screening test.
- Stage II: Tumor is between 1 and 4 cm (between 0.3 and 1.5 in).
- Stage III: Nearby lymph nodes reveal cancer.
- Stage IV: Evidence of distant metastases.

ANAPLASTIC All cases of anaplastic thyroid cancer are considered Stage IV, because this cancer is extremely aggressive.

Treatments

Papillary thyroid cancer can be treated successfully. Follicular thyroid cancer also has a good cure rate but may be difficult to control if the cancer invades blood vessels or grows into nearby structures in the neck. Medullary thyroid cancers are more difficult to control because they often spread to other parts of the body. Anaplastic thyroid cancer is the fastest growing and tends to respond poorly to all treatments.

Like most cancers, cancer of the thyroid is best treated when it is found early by a primary physician. Treatment depends on the type of cancer and its stage. Four types of treatment are used: surgical removal, **radiation therapy**, hormone therapy, and **chemotherapy**.

SURGERY Surgical removal is the usual treatment if the cancer has not spread to distant parts of the body. It is the primary treatment for earlier stage papillary, follicular, and medullary thyroid cancers. The surgeon may remove the side or lobe of the thyroid where the cancer is found (**lobectomy**) or all of it (total thyroidectomy). If the adjoining lymph nodes are affected, they may also be removed during surgery.

RADIATION For papillary and follicular thyroid cancers, radioactive iodine may be used in addition to surgery. In this treatment, the patient would be asked to swallow a drink containing radioactive iodine. Because the thyroid cells take up iodine, the radioactive iodine collects in any thyroid tissue remaining in the body and kills the cancer cells. External beam radiation may also be used if the radioactive iodine is unsuccessful.

For medullary cancers, radioactive iodine is not used. External beam radiation may be used as a palliative therapy. (A palliative therapy is one intended to make the patient more comfortable, not to cure the cancer.)

HORMONE THERAPY When the thyroid gland is removed and levels of thyroid hormones decrease, the pituitary gland produces TSH that would normally stimulate the thyroid gland to make thyroid hormone. TSH also stimulates thyroid cells to grow, and it probably also promotes thyroid cancer growth. Hormone therapy uses hormones after surgery to stop this growth and the formation of new cancerous thyroid cells. To prevent cancerous growth, the natural hormones that are produced by the thyroid are taken in the form of a pill. Thus, their levels remain normal and inhibit the pituitary gland from making TSH. If the cancer has spread to other parts of the body and surgery is not possible, hormone treatment is aimed at killing or slowing the growth of cancer cells throughout the body.

CHEMOTHERAPY For advanced thyroid cancers for which surgery was not an option or that have not responded well to other treatments, chemotherapy may be tried. For advanced papillary, follicular, and anaplastic thyroid cancers, no chemotherapeutic regimen can be considered standard, and several clinical studies may be ongoing for which patients with these cancers may be eligible. For anaplastic thyroid cancer, some chemotherapeutic agents (**doxorubicin**, doxorubicin/cisplatin combination) have effected partial remission in some patients, but not on a large scale. Patients with anaplastic thyroid cancer may also be eligible for ongoing **clinical trials**.

Prognosis

More than 90% of patients who are treated for papillary or follicular cancer will live for 15 years or longer after the diagnosis of thyroid cancer. Eighty percent of patients with medullary thyroid cancer will live for at least 10 years after surgery. Three to seventeen percent of patients with anaplastic cancer survive for five years.

Alternative and complementary treatments

Alternative treatments are treatments used instead of conventional treatments. Complementary therapies are intended to supplement traditional therapies and usually have the objective of relieving symptoms or helping cancer patients cope with the disease or traditional treatments. Common complementary therapies that may be employed by cancer patients are aromatherapy, art therapy, journal therapy, massage, meditation, music therapy, prayer, t'ai chi, and yoga or other forms of exercise, which can reduce

anxiety and increase a patient's feeling of well-being. A well-balanced diet can also enhance a patient's sense of well-being, and can help cancer patients better manage their treatments and the side effects of those treatments.

A powerful phytochemical (a chemical found in plants), lycopene, gives tomatoes their red color and appears to act as an antioxidant. **Antioxidants** such as lycopene help inhibit DNA oxidation (which can lead to certain forms of cancer), repair damaged cells, and scavenge free radicals. (Free radicals are the molecules thought to be responsible for most types of degenerative diseases and aging.) While it is not being suggested that thyroid cancer could be prevented with antioxidants, patients receiving plenty of antioxidants in their diets may feel healthier and more energetic. Lycopene is a normal constituent of human blood and tissues, where it is found in greater concentrations than beta-carotene or any other carotenoid. Tomatoes, including cooked or processed tomatoes, tomato juices, soups, sauces, paste and ketchup, contain more lycopene than any other food. Guava, rose hip, watermelon and grapefruit also contain lycopene.

Other antioxidants are: Vitamin E, Vitamin C, Beta carotene, Lutein, Pycnogenol, Green tea, Grape-seed extract, Alpha lipoic acid, N-acetylcysteine, and Selenium. Pregnant women should consult a physician before taking any medication, and all patients should discuss the complementary therapies and nutritional supplements they are considering with their physician. Some therapies may interfere with patients' prescribed treatments.

Coping with cancer treatment

After thyroid surgery, some patients experience:

- difficulty swallowing
- voice change
- damage to the parathyroid glands

To cope with difficult swallowing, once patients are able to eat after the surgery, many patients start with soft foods, like milkshakes, bananas, applesauce, yogurt, mashed potatoes, and pureed foods. A consultation before the surgery with a dietitian may be helpful, so that the patient can be prepared.

Hoarseness after surgery is usually temporary. Patients may have difficulty hitting high notes when singing, but, the voice change and hoarseness is usually not a major issue for most patients. (Professional singers are advised to discuss their surgery in great detail with their surgeons beforehand.)

If all four parathyroid glands are injured or damaged, it may be necessary for patients to take calcium supplements for a few weeks. Rarely, these supplements may be prescribed for longer periods of time, or even indefinitely.

Thyroid cancers

Cancer type	Characteristics	Prognosis
Papillary	60–80% of thyroid cancers Slow-growing cancer in hormone — producing cells	90% of patients will live for 15 years or longer after diagnosis
Follicular	30–50% of thyroid cancers Found in hormone— producing cells	90% of patients will live for 15 years or longer after diagnosis
Medullary	5–7% of Thyroid cancers Found in calcitonin— producing cells Difficult to control as it often spreads to other parts of the body	80% of patients will live for at least 10 years after surgery
Anaplastic	2% of Thyroid cancers Fastest growing Rapidly spreads to other parts of the body	3–17% of patients will survive for five years

After radioiodine treatment, some patients experience neck tenderness, nausea and stomach irritation, and dry mouth (xerostomia). These side effects are rare, but if they occur, patients can try to eat foods that are easy to digest, drink plenty of water to keep the mouth and throat moist, keep lips moist with lip balm, and patients can try sucking on hard candies to alleviate the dry mouth.

The side effects of chemotherapy are bone marrow suppression causing **anemia** and low platelets. This causes weakness or bleeding. Other problems are **nausea and vomiting**, hair loss (alopecia), and inflammation of the oral mucosa. The symptoms are improved with medications.

Depression, if it occurs, is often temporary and can be managed by counseling and family support. Medication is usually not necessary.

Clinical trials

Seven clinical trials taking place for patients diagnosed with various types of thyroid cancer were studying the effectiveness of radioimmunotherapy and peripheral stem cell transplants, combination chemotherapy (using such drugs as **paclitaxel**, **trastuzumab**, and interleukin-12), and vaccine therapy. Information about current clinical trials is available through the National Institutes of Health.

Prevention

Because most people with thyroid cancer have no known risk factor, it is not possible to prevent this

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Calcitonin—A hormone produced by the parafollicular cells (C cells) of the thyroid. The main function of the hormone is to regulate calcium levels in body serum.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing them.

Hormone therapy—Treatment of cancer by inhibiting the production of hormones such as testosterone and estrogen.

Hyperthyroidism—A condition in which the thyroid is overactive due to overstimulation of the thyroid cells.

Hypothyroidism—A condition in which the thyroid gland is underactive.

Lobectomy—A surgical procedure that removes one lobe of the thyroid.

Radiation therapy—Treatment with high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Total thyroidectomy—A surgical procedure that removes the entire thyroid gland.

QUESTIONS TO ASK THE DOCTOR

- What type of thyroid cancer do I have?
- Has it spread?
- Is my thyroid cancer hereditary? Should other members of my family be tested?
- What treatment do you recommend? Do you recommend a clinical trial?
- What are the advantages, disadvantages, and side effects of this treatment?
- How much experience do you have treating thyroid cancer/performing thyroid surgery?

disease completely. However, the risk for radiation-related thyroid cancer can be reduced by avoiding radiation to the neck when possible, and inherited cases of medullary thyroid cancer can be prevented. If a family member has had this disease, the rest of the family can be tested and treated early. Carriers of the RET mutation may want to consider undergoing prophylactic thyroidectomy at an early age. The National Cancer Institute recommends that every one or two years, a doctor examine anyone who has received radiation to the head and neck during childhood. The neck and the thyroid should be carefully examined for any lumps or enlargement of the nearby lymph nodes. Ultrasound may also be used to screen for the disease in people at risk for thyroid cancer.

Special concerns

Complications of surgery are very rare with experienced surgeons. Sometimes injury to the nerves in the neck can cause a husky voice or difficulty singing high notes. This can be improved with collagen injection after surgery. Occasionally there is bleeding after the surgery and the incision is reopened to evacuate the clot and stop the bleeding. Patients may have a slightly increased risk of developing another cancer (such as leukemia) in the future after undergoing radioiodine treatment, but this correlation has not been proven. Because thyroid cancers may grow slowly and may recur decades after treatment, follow-up care is important.

See also Endocrine system tumors; Head and neck cancers; Multiple endocrine neoplasia syndromes.

Resources

BOOKS

Cameron, John L. *Current Surgical Therapy*. 6th ed. St. Louis: Mosby, Inc., 2001.

ORGANIZATIONS

American Cancer Society. Telephone: 1-800-ACS-2345. Web site: <http://www.cancer.org>.

National Cancer Institute, Cancer Information Service. Telephone: 1-800-4-CANCER (1-800-422-6237). Deaf and hard of hearing callers with TTY equipment may call 1-800-332-8615. Web site: <http://www.nci.nih.gov/>.

OTHER

Clinical Trials.gov. Web site: < http://clinicaltrials.gov/>.

National Institutes of Health. *Eating Hints for Cancer Patients: Before, During, and After Treatment*. NIH Publication #98-2079. Revised July 1997. Also available at: <http://cancernet.nci.nih.gov/peb/eating_hints/>.

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Thyroid nuclear medicine scan

Definition

A thyroid nuclear medicine scan is a diagnostic procedure to evaluate the thyroid gland, which is located in the front of the neck and controls the metabolism of the body. A radioactive substance that concentrates in the thyroid is taken orally or injected into a vein (intravenously), or both. There are three types of radioactive iodine used in these scans. A special camera is used to take an image of the distribution of the radioactive substance in and around the thyroid gland. This is interpreted to evaluate thyroid function and to diagnose abnormalities. Although other imaging methods exist for evaluating thyroid disease, thyroid scanning is the most commonly used and is the most cost-effective.

Purpose

A thyroid scan can help assess the overall structure and function of the thyroid. It can be used to identify benign cancers, to assess nodules, to evaluate masses, to locate the source of a painful gland, to assess gland size, to find differentiated carcinomas, and to identify thyroid tissue. A thyroid scan may be ordered by a physician when the gland becomes abnormally large, especially if the enlargement is greater on one side, or when hard lumps (nodules) are felt. The scan can be helpful in determining whether the enlargement is caused by a diffuse increase in the total amount of thyroid tissue or by a nodule or nodules. The thyroid scan plays a critical role in the diagnosis of **thyroid cancer**.

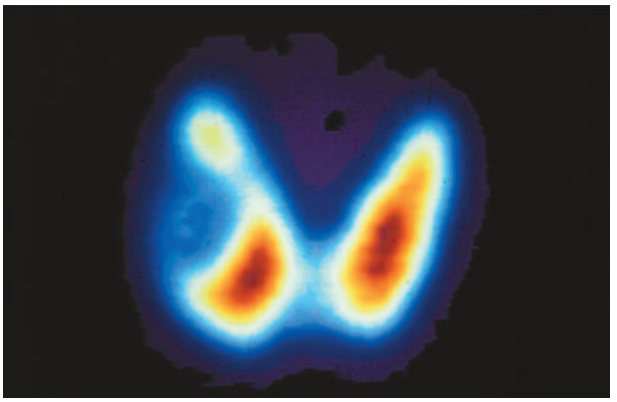
When other laboratory studies show an overactive thyroid (hyperthyroidism) or an underactive thyroid (hypothyroidism), a radioactive iodine uptake scan is often used to confirm the diagnosis. A thyroid scan is often performed in conjunction with this scan. Thyroid radionuclide scanning is being considered as a means to screen individuals at risk for thyroid disease following **radiation therapy**.

Precautions

Women who are pregnant should not have this test. Any person with a history of allergy to iodine, such as those with shellfish allergies, should notify the physician before the procedure is performed.

Description

This test is performed in a radiology facility, either in an outpatient x-ray center or a hospital department. Most often, the patient is given the radioactive substance in the form of a tasteless liquid or capsule. It may be injected into a vein (intravenously) in some instances. Generally, the patient lies on an examination table as the scanning is performed. Images will be taken at a specified amount of time after this, depending on the radioisotope used. Most often, scanning is done 24 hours later, if the radioisotope is given orally. If it is given intravenously, the scan is performed approximately 20 minutes later.



A gamma scan of the human thyroid gland revealing cancer. *(Custom Medical Stock Photo. Reproduced by permission.*

For a thyroid scan, the patient is positioned lying down on his or her back, with the head tilted back. The radionuclide scanner, also called a gamma camera, is positioned above the thyroid area as it scans. This takes 30–60 minutes.

The uptake study may be done with the patient sitting upright in a chair or lying down. The procedure is otherwise the same as described for the thyroid scan. It takes approximately 15 minutes. There is no discomfort involved with either study.

A thyroid scan may also be referred to as a thyroid scintiscan. The name of the radioactive substance used may be incorporated and the study called a technetium thyroid scan or an iodine thyroid scan. The radioactive iodine uptake scan may be called by its initials, an RAIU test, or an iodine uptake test.

Preparation

Certain medications can interfere with iodine uptake. These include certain cough medicines, some oral contraceptives, non-steroidal anti-inflammatory drugs, epilepsy drugs, and thyroid medications. The patient is usually instructed to stop taking these medications for a period of time before the test. This period may range from several days up to three to four weeks, depending on the amount of time the medicine takes to clear from the body.

Other **nuclear medicine scans** and x-ray studies using contrast material performed within the past 60 days

KEY TERMS

Adenoma—A type of non-cancerous tissue that emanates from glands.

Benign—A type of tissue overgrowth that is not progressive, unlike malignant tissue.

Graves' disease—A condition characterized by bulging eyeballs, among other symptoms, that is synonymous with hyperthyroidism.

Radioisotope—A radioactive or radiation-emitting form of an element.

Radionuclide—A substance that emits radiation as it disintegrates.

may affect this test. Therefore, patients should tell their doctors if they have had either of these types of studies before the thyroid scan is begun, to avoid inaccurate results.

Thyroid scan test results can be affected by other conditions, such as kidney failure, cancer, cancer **chemotherapy**, hepatitis, cirrhosis of the liver, infections, trauma, poor nutrition, and mental illness.

Some institutions prefer that the patient have nothing to eat or drink after midnight on the day before the radioactive liquid or capsule is to be taken. A normal diet can usually be resumed two hours after the radioisotope is taken. Dentures, jewelry, and other metallic objects must be removed before the scanning is performed. No other physical preparation is needed.

The patient should understand that there is no danger of radiation exposure to themselves or others. Only very small amounts of radioisotope are used. The total amount of radiation absorbed is often less than the dose received from ordinary x rays. The scanner or camera does not emit any radiation, but detects and records it from the patient.

Aftercare

No isolation or special precautions are needed after a thyroid scan. The patient should check with his or her physician about restarting any medications that were stopped before the scan.

Risks

There are no risks with this procedure.

Normal results

A normal scan will show a thyroid of normal size, shape, and position. The amount of radionuclide uptake by the thyroid will be normal, according to established laboratory figures. There will be no areas where radionuclide uptake is increased or decreased.

Abnormal results

An area of increased radionuclide uptake may be called a hot nodule or "hot spot." This means that a benign growth is overactive. Despite the name, hot nodules are unlikely to be caused by cancer. Increased radionuclide uptake is indicative of hyperthyroidism and may suggest Graves' disease or an active pituitary **adenoma**.

An area of decreased radionuclide uptake may be called a cold nodule, or "cold spot." This indicates that this area of the thyroid gland is underactive. A variety of conditions, including cysts, hypothyroidism, nonfunctioning benign growths, localized inflammation, or cancer, may produce a cold spot. Single nodules that are not functioning are malignant in about 10–20% of cases. Completely nonfunctioning nodules have a higher probability of being malignant than those that have some degree of function.

A thyroid nuclear medicine scan is rarely sufficient to establish a clear diagnosis. A majority of nonfunctioning nodules are not malignant, but their presence increases the probability of a malignancy. Nodules that are functioning are rarely malignant. Frequently, the information revealed will need to be combined with data from other studies to determine the problem.

Resources

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Mark A. Mitchell, M.D.

TNM Staging *see* **Tumor staging**

Topotecan

Definition

Topotecan is a drug used to treat certain types of cancer. Topotecan is available under the trade name Hycamtin, and may also be referred to as topotecan hydrochloride or topotecan HCl.

Purpose

Topotecan is an antineoplastic agent used to treat small cell lung cancer, and certain cancers of the ovary.

As of late 2003, clinical trials are underway in Italy and France to test the effectiveness of topotecan in treating tumors of the brain (glioblastomas) and autonomic nervous system (neuroblastomas). In the French study, topotecan is given together with radiotherapy while the Italian trial uses topotecan as part of combination chemotherapy. Early results indicate that the drug may be useful in treating cancers of the nervous system as well as ovarian and small-cell lung cancers.

Description

Topotecan is a synthetic derivative of the naturally occurring compound camptothecin. Camptothecin belongs to a group of chemicals called alkaloids, and is extracted from plants such as *Camptotheca acuminata*. Captothecin was initially investigated as a chemotherapeutic agent due to its anti-cancer activity in laboratory studies. The chemical structure and biological action of topotecan is similar to that of camptothecin and **irinotecan**.

Topotecan inhibits the normal functioning of the enzyme topoisomerase I. The normal role of topoisomerase I is to aid in the replication, recombination and repair of deoxyribonucleic acid (DNA). Higher levels of topoisomerase I have been found in certain cancer tumors compared to healthy tissue. Inhibiting topoisomerase I causes DNA damage. This damage leads to apoptosis, or programmed cell death.

Topotecan is used in patients whose cancer of the ovary has recurred or progressed after platinum-based treatment such as **cisplatin**. Topotecan is also used to treat relapse of small cell lung cancer that initially responded to other drugs. Increases in survival times have been observed in patients treated with topotecan compared to control populations treated with **paclitaxel**.

Tumors that are targeted by topotecan sometimes develop resistance to the drug. Although the reasons for this resistance are not fully understood as of late 2003, researchers think that they may be related either to inadequate amounts of drug in the tumor or to alterations in topoisomerase I that make the enzyme resistant to topotecan.

KEY TERMS

Alkaloid—A nitrogen containing compound occuring in plants

Anorexia—Loss of appetite and the inability to eat

Apoptosis—An active process in which a cell dies due to a chemical signal. Programmed cell death.

Recommended dosage

Patients should be carefully monitored before and during topotecan treatment for bone marrow function.

Topotecan is administered intravenously over 30 minutes once per day for five consecutive days followed by 16 days of rest. This schedule may be repeated every 21 days. The initial dose of topotecan may be adjusted downward depending on patient tolerance to the toxic side effects of topotecan.

The dose of topotecan may be reduced in patients with kidney dysfunction.

No dose modification is necessary for patients with liver impairment.

No dose modification is necessary for elderly patients.

Precautions

Topotecan should be used only under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Certain complications will only be possible to manage if the necessary diagnostic and treatment resources are readily available. Topotecan should not be used in patients with bone marrow **depression** before starting treatment. Skin that comes in contact with topotecan must be washed thoroughly with soap and warm water.

The dose of topotecan may be reduced in patients with moderate kidney dysfunction. Topotecan is not recommended for use in patients with severe kidney dysfunction.

Topotecan should not be administered to pregnant women. Women of child bearing age are advised not to

become pregnant during treatment. Women should discontinue nursing prior to taking topotecan.

Side effects

Suppression of bone marrow function is the most serious side effect commonly observed in this treatment and can lead to death. Bone marrow reserves should be monitored by blood cell counts for all patients before and during topotecan treatment. The suppression of bone marrow is not cumulative over time. Additional side effects including nausea and vomiting, **anorexia**, **diarrhea**, constipation, headache and hair loss (alopecia) may occur.

Interactions

Suppression of bone marrow is more severe when topotecan is given with platinum drugs. G-CSF (**filgrastim**) may extend the duration of bone marrow suppression. If G-CSF is used, it should not be administered until day six of the 21-day course.

See also Lung cancer, small cell.

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Toremifene

Definition

Toremifene, also known as Fareston, is a synthetic compound similar to estrogen. It mimics the action of estrogen on the bones and uterus, but blocks the effects of estrogen on breast tissue.

Purpose

Toremifene is used as adjuvant hormone therapy immediately after surgery in early stages of **breast cancer** and also to treat advanced metastatic breast cancer (stages III and above) in postmenopausal women. Postmenopausal women at high risk of developing breast cancer may take toremifene to reduce risk.

Description

Toremifene is similar to **tamoxifen** in structure and action. Toremifene can be given as sole treatment, but it is often given in combination with other chemotherapeutic drugs.

Toremifene belongs to a family of compounds called **antiestrogens**. Antiestrogens are used in cancer therapy by inhibiting the effects of estrogen on target tissues. Estrogen is a steroid hormone secreted by granulosa cells of a maturing follicle within the female ovary. Depending on the target tissue, estrogen can stimulate the growth of female reproductive organs and breast tissue, play a role in the female menstrual cycle, and protect against bone loss by binding to estrogen receptors on the outside of cells within the target tissue. Antiestrogens act selectively against the effects of estrogen on target cells in a variety of ways, thus they are called selective estrogen receptor modulators (SERMs).

Toremifene selectively inhibits the effects of estrogen on breast tissue, while mimicking the effects of estrogen on bone (by increasing bone mineral density) and uterine tissues. The former makes toremifene an excellent therapeutic agent against breast cancer. Although researchers are unclear of the precise mechanism by which toremifene kills breast cancer cells, it is known to compete with estrogen by binding to estrogen receptors, therefore limiting the effects of estrogen on breast tissue. Toremifene also may be involved in other anti-tumor activities affecting oncogene expression, promotion of apoptosis and growth factor secretion.

In 2003, clinical trials were underway to test toremifene citrate for treating complications of certain therapies for prostate cancer patients. For example, androgen deprivation therapy results in increased bone fractures

among prostate cancer patients. Researchers believe that toremifene citrate will help reduce these and other effects.

Recommended dosage

Toremifene is taken orally, and the recommended dose is usually 40 to 60 milligrams once a day, although larger doses are sometimes prescribed. If a dose is missed, patients should not double the next dosage. Instead, they should return to their regular schedule and contact their doctor.

Precautions

Toremifene is not recommended for use in children. Women who are pregnant or nursing should not use this drug since it has several side effects that, although rare, can be severe. It is known to cause miscarriages and birth defects. Women are encouraged to use birth control while taking toremifene. However, oral contraceptives can negatively alter the effects of toremifene. Therefore, patients should explore other birth control options.

Great care should be exercised when toremifene is used with **warfarin**, an anticoagulant, because toremifene can amplify the effects of warfarin, prolonging bleeding times. The result could possibly be fatal. Patients who are predisposed to the formation of thromboembolisms should use toremifene with caution, because toremifene can increase the risk.

Side effects

Although toremifene is usually well tolerated by patients, there are some side effects. One of the most serious side effects is development of uterine cancer. Less common effects include eye problems such as retinal lesions, macular edema and corneal changes (most resolve themselves after use is discontinued); neurological problems such as **depression**, dizziness, confusion, and **fatigue**; and genital problems such as vaginal bleeding, vaginal discharge, and endometriosis. Patients also may experience liver problems.

Interactions

Toremifene can interfere with the anticoagulant drug warfarin, resulting in severe consequences and death. If these two drugs are used together, patients will be monitored closely. Oral contraceptives and estrogen supplements can also interfere with the action of toremifene.

See also Raloxifene.

KEY TERMS

Adjuvant—a treatment added to curative procedures such as surgery to prevent the recurrence of cancer

Anticoagulant—an agent preventing the coagulation of blood

Apoptosis—a type of cell death where cells are induced to commit suicide

Granulosa cells—cells that form the wall of the ovarian follicle

Oncogene—a gene whose presence can cause cancer; these genes usually arise through mutation of a normal gene

Ovarian follicle—several layers of cells that surround a maturing egg in the ovary

Thromboembolism—a blood clot that blocks a blood vessel in the cardiovascular system

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Tositumomab

Definition

Tositumomab is a mouse monoclonal antibody that directly targets and binds with the CD20 receptor of normal and malignant B-cell lymphocytes. When linked with iodine I-131, Tositumomab creates an effective radioimmunotherapy agent, Iodine I-131 Tositumomab; also known as the BEXXAR® therapeutic regimen.

Purpose

As part of the BEXXAR@reg; therapeutic regimen, Tositumomab is used in the treatment of patients with CD20 positive, follicular, **non-Hodgkin's lymphoma** (NHL), with or without transformation, whose disease is untreatable with **Rituximab** and has relapsed following **chemotherapy**. Clinical studies of the BEXXAR® therapeutic regimen have shown positive overall response

rates (approximately 63%) and prolonged response durations (upwards of 25 months).

Description

Tositumomab, a monoclonal antibody, can recognize and target the protein produced by the CD20 receptor commonly found on the surface of normal and malignant B-cell lymphocytes. Once injected into the body, the monoclonal antibody seeks out and binds with the CD20 receptor, much as a key fits into a lock. Once attached to the CD20 receptor, the antibody produces a cytotoxic effect and triggers the body's immune system against the cancer cell. This, in turn, exposes the cancer cell, making it more susceptible to radiation. When combined with a radioactive substance, in this case Iodine I-131, the monoclonal antibody allows the ionizing radiation to directly target the cancerous lymphocytes. As lymphomas are particularly vulnerable to radiotherapy, the BEXXAR® therapeutic regimen increases the chance of destroying malignant **lymphoma** B-cells.

The Food and Drug Administration (FDA) approved the Corixa Corporation's BEXXAR® (Tositumomab and Iodine I-131 Tositumomab) therapeutic regimen for the treatment of NHL in June 2003. Clinical studies based on cumulative clinical experience between 1995 and 2005 showed the benefits of the BEXXAR® therapeutic regimen, based on durable responses without evidence of an effect on patient survival.

Recommended dosage

Intended for a single course of treatment, the BEXXAR® therapeutic regimen is administered in two discrete stages over a period of one to two weeks. These stages, the dosimetric stage and the therapeutic stage, are conducted over a period of four hospital visits.

Before treatment begins, and for two weeks subsequent to the therapeutic stage, the patient is provided with daily iodine supplements, typically provided in the form of liquid drops or tablets. The supplements protect the patient's thyroid gland from the radioactive I-131 during the treatment.

At the beginning of the dosimetric stage of the BEXXAR® treatment, paracetamol and antihistamine drips are administered to counteract possible side effects. The patient is provided with a sequential infusion of Tositumomab, totaling 450 mg, over the next hour. This step of the treatment assures that the infusion of Iodine I-131 Tositumomab will spread evenly throughout the patient's body. Finally, an infusion of 35 mg Tositumomab and 5 mCi Iodine I-131 (Iodine I-131 Tositumomab) is administered for 20 minutes. The patient then undergoes the first of three body scans to determine the levels of radioactivity within the patient's body and where it is located. The patient undergoes a second and third body scan at days two to four and days six to seven, respectively. These scans allow the doctor to determine the appropriate dosage for the therapeutic stage of the treatment. This is a complicated evaluation process, and as such, the BEXXAR® treatment is only available to physicians with the required training to make proper assessments.

The therapeutic stage begins on the fourth hospital visit, which typically takes place 7 to 14 days after the dosimetric stage. Once again, the patient is provided with a sequential infusion drip of Tositumomab, totaling 450 mg, over a one-hour period. This is followed by an infusion of Iodine I-131 Tositumomab, consisting of 35mg Tositumomab and a dosage of Iodine I-131 determined by the findings from the dosimetric stage. Additional factors, such as the presence of **thrombocytopenia**, can require the dosage of Iodine I-131 to be reduced.

Precautions

The BEXXAR® therapeutic regimen is contraindicated for patients with known hypersensitivity to murine (mouse) proteins and/or intolerance to thyroid-blocking agents. Patients should be screened for human hypersensitivity antibodies (HAMA) to avoid risk of serious reactions, including anaphylaxis. Patients with impaired hepatic or renal function, impaired bone marrow reserves, and/or more than 25% lymphoma marrow involvement should use caution when considering the BEXXAR® therapeutic regimen, as safety and efficacy have not as of 2005 been clinically established.

Due to the radioactive components of this treatment, the BEXXAR® therapeutic regimen can cause fetal harm and, as such, is contraindicated for pregnant woman. Additionally, an effective contraceptive should be used during and for at least a year following therapy to prevent possible birth defects. Patients wishing to have children should speak with their healthcare provider, as Iodine I-131 tositumomab possesses the risk of toxic effects on male and female fertility.

Patients must strictly follow all safety measures associated with radioactivity during and after therapy, as their bodies will remain radioactive during this time. Healthcare providers will inform their patients of specific safety instructions and their duration. Typical precautions include minimizing close contact (within six feet) with family members. Infants, young children, and pregnant women are particularly susceptible and should be strictly avoided. Nursing is strongly contraindicated, as radioiodine is excreted in breast milk and can build up to levels equal to or greater than those found in the mother.

KEY TERMS

Cytopenias—Disorders which cause a severe deficiency in the production of one or more the blood cell types; red blood cells (anemia), white blood cells (neutropenia), and platelets (thrombocytopenia). Cytopenias can be caused by cancer, chemotherapy, and radiation therapy.

Monoclonal antibodies—Monoclonal antibodies recognize and lock onto the proteins found on the surface of cancer cells. They can cause the cancer cells to destroy themselves, as well as directly target the body's immune system against the cancer cells. This form of passive immunotherapy can even be effective for treating patients with weakened immune systems, as the monoclonal antibodies are mass produced outside the body in a laboratory setting.

Myelodysplasia—A group of disorders in which the bone marrow does not function normally and produces insufficient number of normal blood cells.

Non-Hodgkin's lymphoma—A disease that causes malignant cancer cells to form in the lymphatic system and is unpredictable in nature and more likely to spread to other sites.

Radioimmunotherapy—A treatment modality, in which cytotoxic radiation is delivered directly to a tumor via binding antibodies. Also known as targeted radiotherapy.

Patients should avoid sharing the same bed or using the same hygienic facilities as other people. Finally, prolonged travel (three to four hours) in close proximity to others should be avoided, such as cars, trains, or airplanes. If possible, the patient should remain as far as possible from others during short trips.

Side effects

Clinical studies of the BEXXAR® therapeutic regimen have shown prolonged and severe cytopenias to be the most common adverse reactions, occurring in 71% of the patients studied. Thrombocytopenia and **neutropenia** were the primary forms of cytopenia, documented in 63% and 53% of patients undergoing therapy, respectively. **Anemia** also appeared in 27% of the studied patients. These adverse effects also included the consequences commonly associated with cytopenias, such as infections, hemorrhaging, and the requirement of blood growth factors and/or blood support.

Allergic reactions (angiodema and bronchospasm), **pneumonia**, secondary leukemia, solid tumors, and myelodysplasia were also observed. The most frequent non-hematological adverse effects observed in patients included asthenia (weakness), **fever**, nausea, gastrointestinal symptoms, chills, and pruritus (intense **itching**). Other known side effects include back pain, constipation, **diarrhea**, dizziness, and headache. The BEXXAR® therapeutic regimen is also associated with further risks of infusion-related reactions, delayed-onset hypothyroidism, and HAMA. Health providers should inform patients of these risks before beginning treatment.

Interactions

Although no formal drug interaction studies have been conducted on the BEXXAR® therapeutic regimen, patients should avoid certain drugs unless specifically prescribed by their health provider. These drugs include aspirin, ibuprofen, ketoprofen, and naproxen, as these drugs may mask a fever or increase the risk of hemorrhaging. Additionally, anticoagulants and agents interfering with platelet function may increase the risk of bleeding. Tositumomab may decrease the response to and increase the risk of adverse reactions to live-virus **vaccines**. As such, patients undergoing the BEXXAR® therapeutic regimen are strongly urged to consult with their health provider before undergoing any form of immunization.

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Jason Fryer

Tracheostomy

A tracheostomy is an artificial airway, which is surgically inserted through the windpipe to allow normal respiration.

The key purpose of a tracheostomy is to provide a patient with an open, functional airway. Normal respiration can become hindered or blocked by an obstruction to the upper respiratory tract; the area between the nose and mouth down through the larynx. When a serious obstruction occurs, normal respiratory techniques, such as oral or nasal intubation, may be inadequate or completely ineffective. Obstructions can come from several sources, including foreign bodies, swollen soft tissue, and injury to the larynx and/or trachea. Furthermore, proper respiration can also be obstructed by the growth of malignant tumors in the mouth, larynx, trachea, nasopharynx (the space above and behind the soft palate), and the nasal cavity and paranasal sinuses.

Proper oxygenation of the lungs may also require the use of a tracheostomy. Malignant pulmonary cancers, such as bronchioloalveolar **carcinoma** and **mesothelioma**, can cause serious respiratory problems, including hypoxia (an insufficient oxygen level in the blood and tissues) or hypercapnia (excess levels of carbon dioxide in the blood due to hypoventilation). A tracheostomy can provide the required oxygen levels via the tracheobronchial tree, also known as the bronchia.

A tracheostomy may also be used to clean and remove secretions that build up in the bronchia and throat due to injury, disease, and tumors. This excess fluid can cause obstructions and/or restrict proper oxygenation. Blood and secretions can be suctioned out through the trachea to relieve breathing problems.

There are no known contraindications for the use of a tracheostomy. However, some surgical modalities, such as removal of malignancies, may be required prior to the tracheotomy procedure.

At the simplest level, a *tracheostomy* is an artificial airway that is inserted into the trachea (windpipe) to bypass the upper airway. The surgical procedure to create this secondary airway is known as a *tracheotomy*. Tracheostomies provide physicians with one of the most effective methods to relieving breathing problems due to obstruction. Indeed, historical evidence reveals that tracheostomies may have been used as far back as 2000B.C. Since Antonio Brasavola performed the first documented tracheotomy in the 16th century, surgeons and doctors have been developing and refining this effective medical procedure.

The most common form of tracheostomy is a hollow tube of plastic, silicon, or metal, also known as a tracheostomy tube or trach. During a tracheotomy, this tube is surgically inserted into the patient's neck just beneath the larynx to provide access to the trachea, thus acting as a secondary airway. The surgical opening through which the tracheostomy is inserted is also known as the stoma. Depending on the underlying cause of obstruction and/or respiratory distress, a tracheostomy may be temporary or permanent in nature. Tracheostomies are far more effective for suctioning purposes and maintaining respiratory function than other artificial airways. There are three key types of tracheotomies: *Elective*, *Awake*, and *Emergent*.

- Elective—The majority of tracheotomy procedures are elective in nature. Most patients will have already been intubated by this point in time and may require more prolonged and/or more effective form of intubation. These procedures are conducted under controlled conditions, usually performed in a hospital's operating room under the supervision of a surgeon and anesthesiologist.
- Awake—Acute respiratory distress may require an "awake" tracheotomy. These procedures are typically conducted under controlled conditions and using local anesthesia. However, the patient remains conscious throughout the procedure, which can be extremely disconcerting for the patient. The operating surgeon must be prepared for difficulties caused the heightened levels of anxiety the patient will undoubtedly exhibit.
- Emergent—Emergent tracheotomies, sometimes crudely referred to as "slash" tracheostomies, generally

should not be considered unless the patient is in extremis and intubation is inadvisable. Even in these extreme cases, a cricothyrotomy is more advisable to relieve respiratory distress that a tracheotomy.

There are several variations of the tracheotomy, but follow a basic guideline. Once the patient is anesthetized, either generally or locally, the neck is cleaned and positioned. Surgical incisions expose the tough cartilage rings that form the trachea's outer wall. An incision is made through two of these rings and a tracheostomy tube inserted into the windpipe.

Tracheostomy tubes come in a variety of shape, sizes, and compositions. Tubes are generally designed to meet specific medical requirements, and can be either disposable or reusable in nature. The Universal is most commonly used tracheostomy tube. Also known as the "double-luman" or "double-cannula" tube, the Universal consists of three parts: the outer cannula (with cuff and pilot tube), the inner cannula, and the obturator. Other commonly used tracheostomy tubes include:

- Single cannula (used for patients with long and/or thin necks)
- Fenestrated (allow speech and improve swallow function)
- Tracheostomy Button (used to wean patients before final removal of tracheostomy tubes or in the treatment of sleep apnea)
- Cuffed tube (used commonly when mechanical ventilation is required and prevents aspiration of secretions)
- Cuffless tube (used in long-term management)

If possible, the patient should fully discuss the procedure and other viable opinions with their physician at length before undergoing a tracheostomy. Additionally, cancers of the upper airway and throat may require the use of other surgical procedures beforehand. In these cases, an effective treatment plan incorporating the tracheostomy should be established. Stabilization of precipitating factors may also be required beforehand.

Successful tracheostomies require effective and thorough postoperative care. Patients may require one to three days to breathe normally following the insertion of a tracheostomy tube. The tube may prevent verbal communication for a prolonged period, and other methods of communication should be utilized. All patients with tracheostomy tubes require humidification to prevent further complications associated with inspired gases. Aftercare modalities should strive to accomplish four key goals:

- Maintain the patient's airway
- Maintain tracheal integrity
- Avoid infections
- Avoid tube displacement

Patients and family members should be educated in aftercare modalities and information as soon as possible. Home nursing service may be required for patients. Otherwise, a return to regular home life is encouraged. However, while outdoors, a scarf or similar covering around the throat is indicated.

Directly following the procedure, the trachea will produce excessive secretions due to trauma. In addition to monitoring of these secretions, continual saline irrigation and suctioning will be required. Mucolytic (antimucus) agents can be utilized to prevent dangerous obstructions. Assessment of the patient's vital signs should also be maintained, in addition to monitoring for other complications associated with surgery.

Further complications can be encountered at all stages of recovery following a tracheotomy: *immediate*, *early*, and *late*.

Immediate complications can occur directly following the tracheotomy and include:

- Apnea
- Bleeding
- Pneumothorax (accumulation of air or gas in the pleural cavity)
- Pneumomediastinum (escape of air into the pleural tissues)
- Injury to adjacent structures
- Postobstructive pulmonary edema (accumulation of fluid in the lungs)

Early complications typically occur within seven days of the tracheotomy and include:

- Bleeding
- Mucus obstructions
- Inflammation of the trachea
- Inflammation of subcutaneous or connective tissue around the incision
- Tube displacement
- Subcutaneous emphysema (air or gas in subcutaneous tissues)
- Total or partial collapse of the lung

Late complications can occur at any time seven days following the tracheotomy and can include:

- Bleeding

KEY TERMS

Cricothyrotomy—Aprocedure in which an incision is made through the skin and the cricothyroid-membrane for emergency relief of upper respiratory obstruction, used prior toor in place of tracheotomy.

Larynx—The section of theupper respiratory tract between the pharynx and the trachea.

Trachea—Alsoknown as the windpipe, the trachea is a thin-walled, cartilaginous tubedescending from the larynx to the bronchi.

Tracheobronchial tree —Ananatomical structure in the chest, which appears like an upside-down tree andis composed of the trachea and bronchi.

- Tracheomalacia (degeneration of the elastic and connective tissue of the trachea)
- Tracheoesophageal fistula (an abnormal connection between the trachea and the esophagus)
- Tracheocutaneous fistula (an abnormal connection between the trachea and the surface of the neck)
- Granulation and scarring
- Failure to remove the tracheostomy tube

The normal tracheostomy can be used for days, weeks, and even or years with proper treatment. However, tracheostomy tubes should be downsized and removed as quickly as medically viable. Once the tracheostomy is removed, the stoma is sealed and allowed to heal over a period of five to seven days. Typically, a full recovery can be expected within two weeks with little to no scarring.

Several abnormal results of varying seriousness areassociated with tracheostomies. However, patients should contact localemergency services if their tracheostomy tube is dislodged and cannot bereplaced. Additional concerns include:

- Infection
- Fever
- Chills
- Incision sites problems, such asswelling, increased pain, and excessive bleeding
- Nausea and/orvomiting
- Shortness of breath and/or cough despite suctioning
- Persistent speech difficulties after tracheostomy removal

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Jason Fryer

Transfusion therapy

Definition

The process of transferring whole blood or blood components from one person (donor) to another (recipient).

Purpose

Transfusions are given to restore lost or depleted blood components, to improve clotting time, and to improve the ability of the blood to deliver oxygen to the body's tissues. Typical reasons cancer patients receive blood transfusions are for **anemia** (low red blood cell count) and for clotting factors or platelets (for example, in certain types of leukemia).

Precautions

For donors, the process of giving blood is very safe. Only sterile equipment is used and there is no chance of catching an infection from the equipment. There is a slight chance of infection at the puncture site if the skin is not properly washed before the collection needle is inserted. Some donors feel light-headed upon standing for the first time after donating. Occasionally, a donor will faint. Donors are advised to drink plenty of liquids

to replace the fluid lost with the donation of blood. It is important to maintain the fluid volume of the blood so that the blood pressure will remain stable. Strenuous exercise should be avoided for the rest of the day. Most patients have very slight symptoms or no symptoms at all after donating blood. People who have cancer usually are not considered candidates for blood donation.

For recipients, a number of precautions must be taken by the blood bank. The blood given by transfusion must be matched with the recipient's blood type. Incompatible blood types can cause a serious adverse reaction (transfusion reaction). Blood is introduced slowly by gravity flow directly into the veins (intravenous infusion) so that medical personnel can observe the patient for signs of adverse reactions. People who have received many transfusions (such as leukemia patients) can develop an **immune response** to some factors in foreign blood cells. This immune reaction must be checked before giving new blood. Infectious diseases can also be transmitted through donated blood. However, many safeguards are in place in the United States to minimize the risk of transmission of blood-borne pathogens (agents in the blood that cause disease) to recipients.

Description

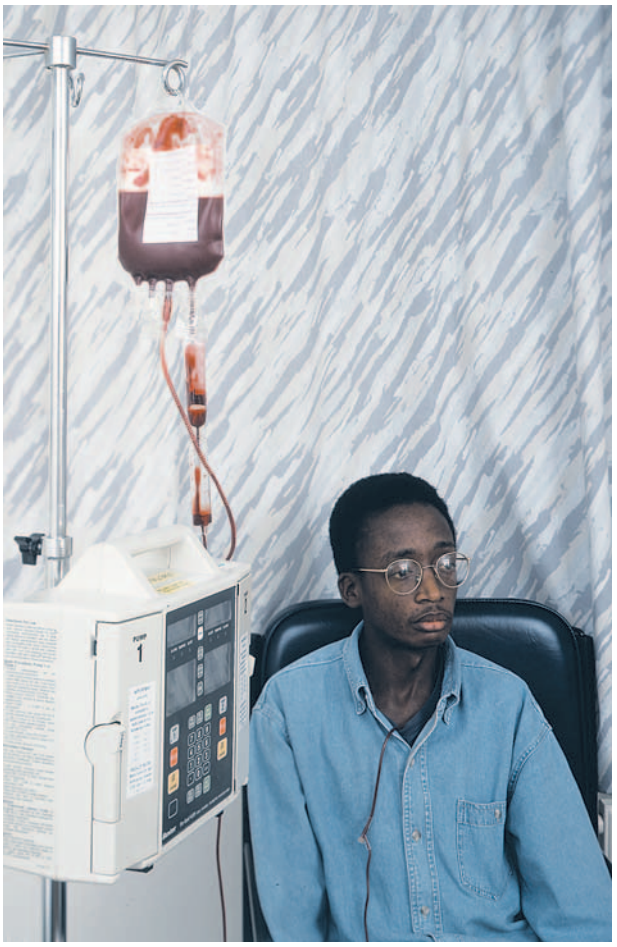
WHOLE BLOOD Either whole blood or blood components can be used for transfusion. Whole blood is used exactly as it was received from the donor. Blood components are parts of whole blood, such as red blood cells (RBCs), plasma, platelets, clotting factors, immunoglobulins, and white blood cells. Whole blood is used only when needed or when components are not available. Most of the time, whole blood is not used because the patient's medical condition can be treated with a blood component. Too much whole blood can fluid-overload a patient's circulatory system. This can create high blood pressure and congestive heart failure (overwork of the heart muscle to pump the extra fluid volume). The use of blood components is more efficient and effective because blood that has been fractionated (processed) into components can be used to treat more than one person.

PLASMA Plasma is the liquid portion of blood. It contains many useful proteins, especially clotting factors and immunoglobulins. After they are processed, plasma or plasma factors (fractions) are usually frozen. Some plasma fractions are freeze-dried. These fractions include clotting factors I through XIII. Some people have an inherited disorder in which the body produces too little of the plasma clotting factors VIII (hemophilia A) or IX (hemophilia B). Transfusions of these clotting factors help people with hemophilia to stop bleeding. Frozen plasma must be thawed before it is used and freeze-dried plasma must be mixed with liquid (reconstituted). In both cases, these blood fractions are usually small in volume and can be injected by syringe and needle.

RED BLOOD CELLS Red blood cells are the blood component most frequently used for transfusion. RBCs are the only cells in the body that transport oxygen. A transfusion of RBCs increases the amount of oxygen that can be carried to the tissues of the body. RBCs that have been separated from the liquid plasma (packed RBCs) are given to people who have anemia (low red cell count) or who have lost a lot of blood. There are many causes of anemia. In cancer, anemia is caused by the destruction of red blood cells by disease, by medications such as **chemotherapy**, or by disease in the bone marrow where red blood cells are produced. To determine how serious the anemia is, the physician will do a CBC (complete blood count) to look at the hemoglobin level (the oxygen-carrying capacity of the red blood cells), and a hematocrit (the percentage of RBCs in a given volume of blood).

PLATELETS Platelets are another component frequently given by transfusion. Platelets are a key factor in blood clotting. The clear fluid that carries blood cells (plasma) also contains blood-clotting factors. The platelets and plasma clotting factors are extracted from donated blood and concentrated for use. These factors are used to treat cancer patients whose bone marrow has been destroyed by disease. Cancer patients may need platelet transfusions when their bone marrow is not producing enough platelets, either because the bone marrow has been damaged by chemotherapy or because it has been replaced by the growth of cancer cells. Dangerous bleeding may occur if the platelet count is too low. However, if there is no evidence of bleeding (no clinical signs of bleeding), platelets may not be given even if the count is low.

IMMUNOGLOBULINS Immunoglobulins, also called gamma globulin or immune serum, are collected from plasma for use in temporarily boosting the immune capability of a patient. White blood cells (WBCs) are another infection-fighting component of the blood. White blood cells are given by transfusion only rarely. Immunoglobulins are the infection-fighting fraction of blood plasma. This blood fraction is given to people who have difficulty fighting infections, especially people whose immune systems are depressed by diseases, such as HIV/AIDS and cancer. Immmunoglobulins are also used to prevent tetanus after cuts, to treat animal bites when rabies infection is suspected, or to treat severe childhood diseases. Immunoglobulins can also be used to treat idiopathic thrombocytopenic purpura (ITP), a condition characterized by a low platelet count and excessive bruising.



This boy is receiving a transfusion for sickle cell anemia. Cancer patients may receive blood transfusions to treat anemia, or to receive clotting factors or platelets (in certain types of leukemia, for example). *(Custom Medical Stock Photo. Reproduced by permission.)*

COLONY-STIMULATING FACTORS OR GROWTH FACTORS Granulocytes are a type of white blood cell that fight infection. Granulocyte transfusion is no longer done because of the **fever** it produces and the potential transmission of infectious diseases through white cells. These infections (CMV or cytomegalovirus) would be particularly dangerous to a cancer patient with a weakened immune system. Chemotherapy patients can develop a low WBC (white cell count). A specific white blood cell called the neutrophil is carefully monitored because it is very important in fighting multiple types of infection. If neutrophil counts are very low, the physician may order special medications that stimulate the production of neutrophils in the bone marrow. These medicines are called colony-stimulating factors or growth factors, and include granulocyte colony-stimulating factor (G-CSF, or filgrastim), granulocyte macrophage colony-stimulating factor (GM-CSF, or sargramostim), and interleukin-3.

ALTERNATIVES TO BLOOD TRANSFUSION Researchers have been working to develop a substitute for blood that will avoid the risks associated with blood transfusion. Products are being developed that will perform the functions of red blood cells, such as carrying oxygen through the blood stream, but there is no real substitute for the transfusion of human blood. Two products that are currently available are known as hemoglobin-based oxygen carriers and perfluorochemical compounds. These products can be used on a short term basis to perform the function of blood, but are still considered experimental.

Other types of products that can help patients in need of large volumes of body fluids are volume expanders such as normal saline solution, lactated ringers, or dextran. These are IV (intravenous) solutions that can replace lost fluid volume but not the red blood cells' function of carrying oxygen to the body. Other volume expanders include albumin, a protein solution used to stabilize oncotic pressure (pressure within the veins) and prevent or treat shock. Growth factors, as mentioned earlier, help promote the production of specific white cells needed to fight infections. **Erythropoietin** and **thrombopoietin** are products available to help stimulate the production of red blood cells and platelets. None of these products replace the benefits of blood or blood component transfusions.

New cancer treatments under research

Researchers are looking at the efficacy of using sibling blood components, specifically transfusions of stem cells and T cells, a part of the immune system that can attack and destroy cancer cells. Blood from tissue-matched sibling donors reduces the rejection rate by the patient's body chemistry. This technique is being studied in renal (kidney) tumors, and early results show promise. Researchers are particularly interested in this therapy for renal tumors with **metastasis** (spreading of the cancer to other parts of the body) because this type of cancer does not usually respond to standard cancer therapy protocols. While blood transfusions and bone marrow transplants have been used extensively for cancers of the blood, this is the first time transfusions have been successful in the treatment of solid tumors (such as renal tumors).

Researchers are also looking at the placenta and umbilical cord as a source for blood stem cells for transplant. This method is called cord blood transplantation. It offers an alternative for patients who do not have a sibling donor, or cannot locate a match in the National Marrow Donor Program (NMDP) registry.

Blood donation

Each year in the United States, about 14,000,000 pints of blood are donated. Blood collection is strictly

regulated by the Food and Drug Administration (FDA). The FDA has rules for the collection, processing, storage, and transportation of blood and blood products. In addition, the American Red Cross, the American Association of Blood Banks, and most states have specific rules for the collection and processing of blood. The main purpose of regulation is to ensure the quality of blood and to prevent the transmission of infectious diseases through donated blood. Before blood and blood products are used, they are extensively tested for infectious agents, such as hepatitis and HIV/AIDS. Screening prevents blood donation by people who could transmit diseases or by people whose medical condition would place them at risk if they donated blood. Some geographical areas or communities have a high rate of hepatitis or HIV/AIDS. Blood collection in most of these areas has been discontinued.

SPECIAL DONATIONS: AUTOLOGOUS TRANSFUSION Autologous transfusion is a procedure in which patients donate blood for their own use. Patients who are to undergo surgical procedures for which a blood transfusion might be required may elect to donate a store of blood for the purpose ahead of time. The blood is stored at the hospital for the exclusive use of the patient. This procedure assures that the blood type is an exact match. It also assures that no infection will be transmitted through the blood transfusion. This is most helpful to cancer patients because of the reduction of risk for a transfusion reaction and for infection risks associated with transfusions. As with other forms of specialized blood donations, there is a processing fee for collection and delivering each unit of blood, which may not be reimbursed by **health insurance**.

SPECIAL DONATIONS: DIRECTED DONATION Directed donors are family or friends of the patient who needs a transfusion. Some people think that family and friends provide a safer source of blood than the general blood supply. Studies do not show that directed donor blood is any safer. Blood that is not used for the identified patient becomes part of the general blood supply.

SPECIAL DONATIONS: APHERESIS Apheresis is a special procedure in which only the necessary components of a donor's blood are collected. The remaining components are returned to the donor. A special blood-processing instrument is used in apheresis. It separates the blood into components, saves the desired component, and pumps the other components back into the donor. Because donors give only part of their blood, they can donate more frequently. For example, people can give almost ten times as many platelets by apheresis as they could give by donating whole blood.

KEY TERMS

ABO blood groups—A system in which human blood is classified by whether the red blood cells contain A or B antigens. Type A blood has the A antigen; type B has the B antigen, AB has both, and 0 has neither.

Antibody—A simple protein produced by the body to destroy bacteria, viruses, or other foreign bodies. Production of each antibody is triggered by a specific antigen.

Antigen—A substance that stimulates the immune system to manufacture antibodies (immunoglobulins). The function of antibodies is to fight off intruder cells, such as bacteria or viruses, in the body. Antigens stimulate the blood to fight other blood cells that have the wrong antigens. If a person with blood type A is given a transfusion with blood type B, the A antigens will fight the foreign blood cells as though they were an infection.

Immunoglobulin—An antibody.

Infusion—Introduction of a substance directly into a vein or tissue by gravity flow.

Injection—Forcing a fluid into the body by means of a needle and syringe.

Rh (rhesus) factor—An antigen present in the red blood cells of 85% of humans. A person with Rh factor is Rh positive (Rh+); a person without it is Rh negative (Rh-). The Rh factor was first identified in the blood of a rhesus monkey.

Preparation

The person receiving a transfusion is made comfortable and vital signs (temperature, blood pressure, pulse and respirations) are monitored closely. The site where the needle will be inserted is carefully washed with a soap-based solution, followed by an iodine-containing antiseptic. The skin is then dried and the transfusion needle inserted into the recipient's vein. During the early stages of a transfusion, the recipient is monitored closely to detect any adverse reactions. If no signs of adverse reaction are evident, the patient is monitored routinely for the duration of the transfusion period. Upon completion of the transfusion, a pressure bandage is placed over the needle-insertion site to prevent bleeding.

Aftercare

Recipients of a blood transfusion have their vital signs monitored during and after the transfusion for signs

QUESTIONS TO ASK THE DOCTOR

- Am I a candidate for autologous transfusion?
- Am I a candidate for a directed donation?
- How often will I have blood work done to determine my hemoglobin and hematocrit levels?
- Can I get a stem cell transfusion at this facility if I need one?
- Is a blood transfusion necessary before I have surgery?

of adverse reaction. The physician usually orders laboratory tests to check hemoglobin and hematocrit levels, as well as platelet count once the transfusion has ended. This data will help the physician determine if the transfusion of blood or blood products was sufficient.

Risks

Adverse reaction to mismatched blood (transfusion reaction) and transmission of infectious disease are the two major risks of blood transfusion. Transfusion reaction occurs when antibodies in the recipient's blood react to foreign blood cells introduced by the transfusion. The antibodies bind to the foreign cells and destroy them (hemolytic reaction). Transfusion reaction may also cause a hypersensitivity of the immune system that, in turn, may cause tissue damage within the patient's body. The patient may also have an allergic reaction to mismatched blood. The first symptoms of transfusion reaction are a feeling of general discomfort and anxiety. Breathing difficulties, flushing, a sense of pressure in the chest, and back pain may develop. Evidence of a hemolytic reaction can be seen in the urine, which will be colored from the waste of destroyed red blood cells. Severe hemolytic reactions are occasionally fatal. Reactions to mismatches of minor factors are milder. These symptoms include itchiness, dizziness, fever, headache, rash, and swelling. Sometimes, the patient will experience breathing difficulties and muscle spasms. Most adverse reactions from mismatched blood are not life-threatening.

Although transfusions are often necessary, some studies have noted a poorer prognosis if transfusions are done before surgery for **breast cancer**, **colon cancer**, non-small cell lung cancer, and **sarcomas**. A National Institutes of Health (NIH) consensus was that transfusion before surgery should not be given simply to raise the hemoglobin level above 10g/dl. The growth factor erythropoietin may be used more in the future to decrease the need for red blood cell transfusions.

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John T. Lohr

Transitional care

Definition

According to the National Cancer Institute (NCI), transitional care may refer either to a patient's movement from one level of cancer care to another, or from one place of care to another. Levels of cancer care are defined as active (intended to cure the cancer), supportive (intended to relieve discomfort associated with the symptoms of the cancer or the side effects of treatment), or palliative (intended to manage pain when cure is no longer possible). Places of care are categorized as acute care facilities, subacute care facilities (e.g., rehabilitation centers, nursing homes, and hospices), and home care (usually the patient's or family's house).

Description

Transitional care for cancer patients has become a pressing health care issue in the early 2000s. One reason is that health care in the United States and Canada has become increasingly specialized in terms of facilities as well as care givers; in addition, the NCI states that almost 90 percent of care for cancer patients is now given on an outpatient basis. In an acute care hospital or cancer center, a cancer patient may have a health care team that consists of three or more doctors in various medical and surgical specialties as well as nurses, physical therapists, social workers, nutritionists, and others. As the patient undergoes various forms of cancer therapy, his or her response to treatments as well as financial concerns, family issues, and other considerations may lead to transfer to a subacute care facility or to home care.

Another factor that has led to a new understanding of the importance of transitional care is the growing number of long-term survivors of cancer. Although these people may be able to live at home by themselves or return to work, they still require various types of follow-up to monitor the long-term physical and psychological side effects of the cancer treatment they received.

Because of the growing complexity of cancer treatment and the risk that the patient's care may be fragmented or interrupted by changes in caregivers or facilities, medical professionals and policy makers presently emphasize the importance of integrated or "seamless" care. This concern for continuity is reflected both in the NCI's recommendations about changes in patient care and in its use of the biopsychosocial model of health care. The biopsychosocial model is the medical term for understanding the patient as a human being with thoughts, emotions, spiritual needs, and important relationships with family members and friends as well as physical symptoms related to the cancer. The NCI recommends the use of community liaison nurses and social workers as coordinators of patient care in order to relieve the patient or family members of the stress of relaying information from one health care professional to another, and to prevent the patient's care from being i! nterrupted or weakened during transfers from one care facility to another.

The biopsychosocial model is the basis for the comprehensive assessment that precedes planning for transitional care. The patient's health care team will evaluate his or her needs in each of the following areas:

- Physical. This area includes nutritional status, ability to function, smoking history, and future treatment options as well as the current stage of the patient's disease and symptom profile.
- Demographics of the patient and his or her family. This area includes marital status, other family members at home, primary language, cultural background, and educational level.
- Psychological. This part of the assessment covers the patient's (and family members') attitudes toward the cancer, fears and anxieties, habitual coping patterns, history of psychiatric illness, and overall level of family stability.
- Social. This area includes the patient's social support networks, employment history, insurance coverage, availability of transportation, and the patient's knowledge and use of resources in the community.
- Spiritual. This part of the assessment includes the patient's religious beliefs and the level of importance of religion in their life, the extent of their support network in their faith community, and the ways in which their religious beliefs or practices may affect their cancer treatment.
- Legal. This area concerns such matters as the patient's will, estate planning, living will, end-of-life care directives, etc.

This comprehensive assessment should be made at regular intervals during the patient's treatment in order to make any necessary adjustments due to changes in the patient's physical symptoms and level of functioning, family situation, employment, etc.

KEY TERMS

Biopsychosocial model—A way of evaluating a patient that stresses the importance of considering his or her thinking processes, emotions, and social relationships as well as the physical aspects of his or her disease. The biopsychosocial model was first proposed in 1977 by an American psychiatrist named George Engel.

Hospice—A health care facility for supportive and palliative care of people with a terminal disease.

Special concerns

The NCI notes that some groups of cancer patients are at risk of not receiving adequate treatment planning or transitional care. These patients include low-income and homeless people; members of minority groups living in the inner city; and people living in rural areas.

Treatments

The treatments given during transitional care are highly individualized; they depend on the specific

QUESTIONS TO ASK YOUR DOCTOR

- What types of care will I need after I leave the hospital?
- Can I have these services delivered to my home, or must I go to a special facility of some kind?
- Is there someone you would recommend as a transitional care coordinator?
- How much experience do you have in following patients through transitions in their health care?

patient's health status, type of cancer, and the types of treatments (surgery, **chemotherapy**, radiotherapy, etc.) that he or she received in the acute care hospital or cancer center. Advances in medical technology, however, have increased the range and variety of treatments that can be delivered by visiting health care professionals in the patient's home. These advances make transitional care at home a possibility for many cancer patients in the early 2000s.

Alternative and complementary therapies

It is usually possible to integrate CAM therapies into transitional care, provided that the patient discusses the specific alternative treatments desired with his or her doctor. Some types of movement or massage therapy may not be suitable immediately following surgery, however, while some herbal preparations or traditional Chinese medicines may interact with the drugs given to treat the cancer itself or to relieve the side effects of treatment.

Patient participation

In addition to consulting with a social worker or other professional coordinator, patients and their families should be actively involved in planning for transitional care. They can gather information about various therapies, care facilities, local support groups and other resources, and discuss these among themselves as well as with members of the patient's treatment team. The patient and his or her family should not hesitate to ask questions or bring up issues that are not mentioned by the health care team during the patient's evaluation for transitional care. A new interactive resource that may be helpful to many patients in making decisions about treatment is the NexProfiler Tool for Cancer on the ACS website. The patient chooses a specific type of cancer from a menu, which then allows him or her to locate a detailed analysis of that cancer, statistics about treatment types, and topics for discussion with his or her doctor.

See also Psycho-oncology.

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Rebecca Frey, PhD

Transitional cell carcinoma

Definition

Transitional cell carcinoma (TCC) is a type of cancer that usually originates in the kidney, bladder, or ureter (the tube that carries urine from the kidney to the bladder). It has also been recently recognized as a subtype of ovarian cancer.

Description

A transitional cell is intermediate between the flat squamous cell and the tall columnar cell. It is restricted to the epithelium (cellular lining) of the urinary bladder,

ureters (tubes that carry urine from the kidneys to the bladder), and the pelvis of the kidney (that portion of the kidney collecting the urine as it leaves the kidneys and enters the ureters). Transitional cell carcinomas have a wide range in their gross appearance depending on their locations. Some of these carcinomas are flat in appearance, some are papillary (small elevation), and others are in the shape of a node. Under the microscope, however, most of these carcinomas have a papillary-like look. There are three generally recognized grades of transitional cell carcinoma. The grade of the carcinoma is determined by particular characteristics found in the cells of the tumor. Transitional cell carcinoma typically affects the mucosa (the moist tissue layer that lines hollow organs or the cavity of the body) in the areas where it originates.

The most common site of transitional cell carcinoma is in the urinary bladder. Transitional cell carcinoma is the form of cancer in about 90% of cancers found in the bladder. The highest grade of transitional cell carcinoma is very likely to spread to other parts of the body. There are two primary ways that transitional cell carcinoma spreads into the surrounding structures. The first is by way of epithelial cells that line the body cavity and many of the passageways that exit the body. The other means of spread is through the lymphatic (network that resembles the circulatory system but transports proteins, salts, water, and other substances) system.

Demographics

Most patients who develop transitional cell carcinoma are older than 40 years of age; the peak age of incidence is 60–70 years of age. The male:female ratio for this type of cancer is about 5:2. About 93% of all bladder cancers in North American are of the transitional cell carcinoma type. Only 8% of all renal cancers are of the transitional cell carcinoma type. According to the American Cancer Society (ACS), 60,240 Americans will be diagnosed with bladder cancer in 2004 and 12,710 will die from the disease.

Causes and symptoms

The causes and mechanisms of transitional cell carcinoma, like all forms of cancer, are not entirely known or understood. However, researchers have isolated several factors that have been associated with an increased risk for developing this carcinoma.

Cigarette smoking is the strongest risk factor for transitional cell carcinoma. Researchers have found smoking increases the risk for developing this condition by three to seven times. In men with **bladder cancer**, 50% to 80% have a history of smoking **cigarettes**. Other methods of using tobacco, such as cigar and pipe smoking and chewing tobacco, have been shown to increase the risk of developing this carcinoma but at a reduced rate compared with smoking.

Individuals who have undergone long-term exposure to industrial chemicals, such as the class of compounds known as arylamines, are known to have an increased risk of developing transitional cell carcinoma. One of the most dangerous of these chemicals is one known as 2-naphthylamine. Individuals who develop these carcinomas usually do so anywhere from 15 to 40 years following the first exposure to these chemicals. Arsenic is another chemical that has been recently implicated in the development of TCC.

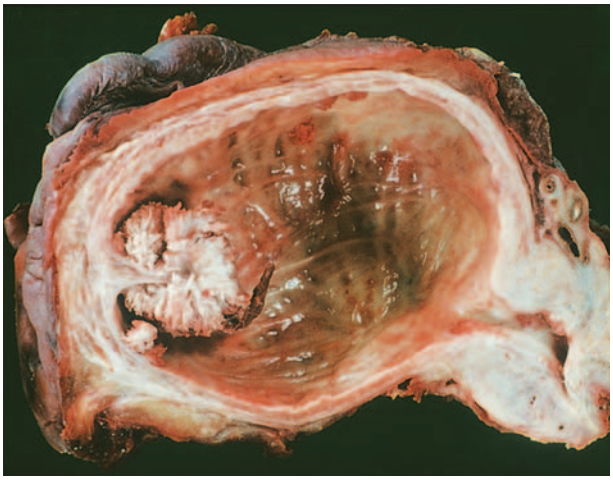
Individuals who have used analgesics for many years, or have used them excessively in the short-term, are at an increased risk for developing transitional cell carcinoma. Many of these patients have suffered at least some damage to the kidneys before developing the carcinoma. Drugs given to patients to treat an earlier cancer, such as the commonly used **cyclophosphamide**, increase the risk of developing transitional cell carcinoma at a later time.

Researchers believe these factors somehow alter genes that are important in the development of transitional cell carcinoma. These changes most often involve the deletions of certain chromosomes but also may result from mutations.

The most common symptom of transitional cell carcinoma is blood in the urine without accompanying pain. There may also be changes in the urge for the patient to urinate and in the frequency of urination. In some cases, urine may be partially obstructed by a tumor in the ureter. Rarely, pain occurs in the pelvic region. Physicians rarely detect a tumorous mass by touch during the first examination.

Diagnosis

There are a variety of ways that can be used to help diagnose transitional cell carcinoma. Many of these involve the use of **imaging studies**. In some cases, traditional x rays may be used to image upper urinary tract tumors. One of the things that physicians look for in patients suspected of having transitional cell carcinoma is the abnormal filling of structures in the urinary system. A type of imaging called excretory urography can help detect such flaws in the system. A different imaging method called retrograde urography can help physicians image the process of urinary collection and detect irregularities. **Computed tomography** (CT), more commonly called the CAT scan, is a very useful tool in the imaging of tumors in the upper tract of the urinary system. CT is



Transitional-cell carcinoma. Seen arising from the dome of the bladder as a fronded cauliflower-like lesion. *(Copyright Biophoto Associates, Science Source/Photo Researchers, Inc. Reproduced by permission.)*

more sensitive than traditional x rays. In some cases, however, small tumors can be missed using this method.

Ultrasound may also be used to help tell the difference between tumors and normal structures in this region. **Magnetic resonance imaging**, more commonly referred to as MRI, has not been found to have any significant advantage over computed tomography in the diagnosis of transitional cell carcinoma.

Cystoscopy is the examination of the bladder using a cystoscope, an instrument that allows the interior imaging of the ureter and bladder. Cystoscopy is usually mandatory in patients suspected of having transitional cell carcinoma and can be helpful in determining the origin of the bleeding in these patients. Patients who are suspected of having transitional cell carcinoma, or other type of cancer in the upper urinary tract, need to have laboratory analysis of the cells in the suspected mass. This cell analysis tells the physician what type and stage of cell is present.

The easiest but least accurate way to study these cells is to have the patient provide urine samples. Patients who have a low-grade tumor in the upper urinary tract will have normal results in up to 80% of cases when urinalysis is used. However, such urinalysis can be more effective in diagnosis of bladder tumors. Obtaining urine samples from the upper urinary tract using a catheter can provide more accurate analysis of upper urinary tract tumors.

A technique called the brush **biopsy** involves the placing of a tiny brush into a catheter. The catheter is then placed in the ureter and moved into the upper urinary tract where the brush scrapes off cells for later analysis. More modern techniques of imaging and sampling use tiny tubes with attached videocameras called endoscopes. These tubes can be moved into the upper urinary tract to locate bleeding and tumors and can be used to obtain biopsy samples.

Treatment team

The treatment team that treats the patient with suspected and confirmed transitional cell carcinoma usually involves a primary care physician who refers to a specialist, a specialist such as a urologist or nephrologist (kidney specialist), a radiologist who performs the imaging, a pathologist who studies the sampled cells, an oncologist who monitors the overall course of the cancer, and a surgeon who performs the surgical removal of the carcinoma.

Clinical staging, treatments, and prognosis

The International Society of Urological Pathology has developed a classification scheme for grading transitional cell carcinoma. These four grades are urothelial papilloma, urothelial neoplasms of low malignant potential, low-grade urothelial carcinoma, and high-grade carcinoma. Papilloma is usually seen in younger patients and is rare. Neoplasms of low malignant potential are sometimes difficult to differentiate from low-grade urothelial carcinomas. These tumors rarely become invasive to nearby tissue. Low-grade urothelial carcinoma tends to appear in the form of papillomas as well. These tumors can invade nearby tissue but usually do not progress. High-grade carcinomas are flat, papillary, or both. These tumors are larger and are more likely to invade nearby muscle tissue.

The most common means to treat papillary transitional cell carcinoma in the bladder is with surgery. When these tumors are classified as low grade, they can typically be removed completely. Unfortunately, these carcinomas recur 50% to 70% of the time. Because of this high rate of cancer recurrence, patients with transitional cell carcinoma have to be carefully monitored following surgery with cystoscopy and regular urinalysis.

Other types of therapy called immunologic therapy (immunotherapy) and **chemotherapy** are often used in treating bladder carcinoma. These methods use agents that are directly applied to the bladder. The most commonly used agent in these therapies is called bacillus Calmette-Guérin (BCG). When BCG is placed in the bladder, the body begins an **immune response** that sometimes destroys the tumor. Patients usually receive one treatment per week for six weeks. After this period, a maintenance program involving three-week BCG courses of treatment for up to two years is used. The most common chemotherapy used for transitional cell

carcinoma in the past is a combination of the drugs **cisplatin**, adriamycin, **vinblastine**, and **methotrexate**. Newer and less toxic drugs, such as celecoxib, bortezomib, ixabepilone, and gallium maltolate are being tested to replace these older agents. A combination regimen of chemotherapy and radiation is being considered as a therapy when the carcinoma invades the muscle surrounding the bladder. The effectiveness of this method has not been studied yet in research studies. **Radiation therapy** alone is not an effective treatment.

Transitional cell carcinoma in the upper urinary tract is also treated with surgical procedures. Affected areas in this region, including the kidney, are sometimes removed. Part or all of the ureter and parts of the bladder are also removed, in some cases.

The noninvasive papilloma rarely recurs once removed. If urothelial neoplasms of low malignant potential recur, they are usually benign tumors. However, in about 3% to 5% of cases, these recurrences are of a higher grade. These carcinomas rarely become invasive, and patients with them have a one-year survival rate of 95% to 98%. Low-grade urothelial carcinomas often show signs of invasion during diagnosis, but are not associated with a high risk for malignancy. High-grade carcinomas have considerable invasiveness into nearby tissue, particularly muscle, and are associated with a very high risk for **metastasis** (movement of cancer cells from one part of the body to another).

Those with superficial, noninvasive, or nonmalignant disease should receive a cystoscopy and a thorough examination every three months for two years followed by a regimen every six months for an additional two years. In those with advanced disease but who did not receive complete bladder removal, a cystoscopy with a thorough examination should be performed every three months for two years, followed by every six months for an additional two years, and then one per year. These patients should also receive a computed tomography (CT) scan of the pelvis and abdomen every six months for two years. Chest x rays, liver function tests, and serum creatinine tests should also be performed on this schedule. Those who had bladder removal should have chest x rays, liver function tests, computed tomography scan of abdomen and pelvis, and serum creatinine tests performed every six months for two years. In addition, an endoscopy of the newly formed bladder structure should be performed.

Coping with cancer treatment

A variety of issues need to be considered when the patient is receiving cancer treatment. One of the most important of these issues is the ability to cope with the emotion of having cancer in the first place. Several techniques, such as relaxation training, meditation, and biofeedback, may be beneficial to the patient in reducing anxiety. Other issues such as missed work and other daily activities need to be planned before the treatment period to reduce emotional stress. The patient needs to consider worst-case scenarios, such as side effects from chemotherapy, when planning these future events. Participation in cancer support groups helps many patients with the stress of the treatment period.

There are physical issues as well during this period. Pain following surgery can be a significant problem. Fortunately, there are many effective pain medications available to handle most pain events. Nausea and hair loss (alopecia) are two of the more notable effects of chemotherapy. Nausea can be effectively treated with drugs in most cases. Hair loss is only a temporary event, but it often has significant psychological effects that can be somewhat alleviated through social support.

Clinical trials

As of 2004 the National Cancer Institute (NCI) lists 46 clinical trials in progress for treating bladder cancer.

KEY TERMS

Analgesic—Drug that relieves pain.

Arylamine—Radical group of the amine chemical family.

Benign—Not progressing or malignant.

Biopsy—Removal of a small piece of living tissue for examination.

Bladder—Muscular and membranous reservoir for urine.

Catheter—Tube that is passed through the body for injecting or removing fluids from body structures.

Chromosomes—Thread in the nucleus of the cell that contains DNA.

Creatinine—End product of creatine metabolism that is found in increased levels in advanced kidney disease.

Immunotherapy—Enhancement of the body's immunity, usually through a biologic agent.

Papilloma—Benign tumor of epithelial tissue.

Tumor—Spontaneous new tissue growth that can be benign or malignant.

Urothelial—Epithelial cells that line the urinary system.

QUESTIONS TO ASK THE DOCTOR

- What type of type of tests are necessary to make an accurate diagnosis?
- Are these tests painful?
- How long will it take to get results?
- If the tests are positive for cancer, what happens then?
- If it is transitional cell carcinoma, is the tumor invasive?
- Has the carcinoma spread to other tissues?
- What stage is the carcinoma?
- What treatment alternatives are there?
- If surgery is necessary, what will the surgery entail?
- What is the recuperation period like after the surgery?
- How long will I be in the hospital?
- If radiation is necessary, what sort of side effects are common?
- If chemotherapy or immunotherapy is necessary, what side effects are common?
- Will chemotherapy cause my hair to fall out?
- Are there any clinical trials that I can participate in?
- What type of surveillance schedule will I be on following the initial surgery and therapy?

Several new drugs are being tested, as well as various combinations of drugs, surgery, and BCG therapy. The best way to obtain the most current information is to call the Cancer Information Service at (800) 4-CANCER. The Cancer Information Service is part of CancerNet, a service of the National Cancer Institute. It can also be accessed at <http://cancernet.nci.nih.gov>.

Prevention

Cigarette smoking is a major risk factor for the development of transitional cell carcinoma. Cigarette smoking has been associated with 25% to 65% of all cases of bladder cancer. Smokers are two to four times more likely to develop transitional cell carcinoma than nonsmokers. Smoking increases the risk of developing tumors that are at a higher grade, in greater number, and of larger size. Those individuals who have abused analgesics are at an increased risk for developing transitional cell carcinoma. Exposure to the human papillomavirus type 16 also increases the risk of developing transitional cell carcinoma. Petroleum, dye, textile, tire, and rubber workers are at increased risk for developing this carcinoma. Exposure to chemicals, such as 2-naphthylamine, benzidine, 4-amino-biphenyl, nitrosamines, or O-toluidine can also increase the risk of developing transitional cell carcinoma. Eliminating exposure to these substances substantially reduces the risk of developing transitional cell carcinoma.

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National Cancer Institute. National Institutes of Health. Bethesda, MD 20892. (800) 422-6237. <http://www.nci.nih.gov>.

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American Pain Society. 4700 West Lake Ave., Glenville, IL 60025. (847) 966-5595.

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Trans-rectal ultrasound *see* **Endorectal ultrasound**

Transvaginal ultrasound

Definition

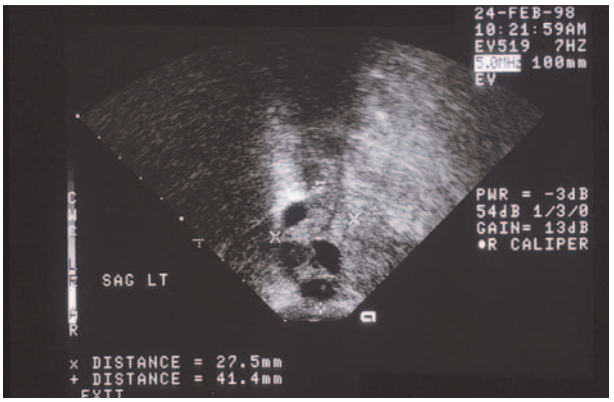
A transvaginal ultrasound, also called transvaginal sonogram (TVS), is an ultrasound that uses an internal probe, or transducer, that enters the vaginal cavity. Either a radiology technician or physician performs the test, and a radiologist interprets the results.

Purpose

An internal probe allows for closer access to the structures that need evaluation. With closer access, higher frequency sound waves can be used, which provides a clearer image due to better resolution. It is often used to evaluate suspected cancer or abnormal growths in the female reproductive system.

Precautions

While the transvaginal ultrasound produces a clearer image, it may also create false positive results. This can lead to unnecessary testing to further evaluate the condition, with its accompanying physical and emotional impact.



Normal transvaginal ultrasound. The plus marks and x marks show that measurements were taken. Measurements of internal structures, such as ovaries, are often taken to compare one ovary with the other, or to compare this woman's ovaries with other women her age, in order to detect possible abnormal growths. *(Custom Medical Stock Photo. Reproduced by permission.)*

Description

The transvaginal ultrasound uses a small, wand-like transducer, or probe, which is inserted into the vagina. The probe emits high-frequency sound waves, which are not audible by humans. These sound waves painlessly bounce off the structures in its path. The returning echo wave is picked up by the probe. This information is fed into an attached computer that then creates an image, or sonogram, on a screen. It can differentiate between structures that are solid, such as a tumor, or filled with fluid, such as a cyst. It can be used to measure the thickness of the lining of the uterus, as well as of other organs.

A technique called color flow Doppler imaging may be used to evaluate the blood flow to certain structures. This can be helpful in establishing whether blood flow has been obstructed or enhanced to an organ. It cannot tell if a solid mass is malignant or benign. Other tests, such as a **biopsy**, would be needed to gather that information. It is done on an outpatient basis, is less expensive than imaging tests such as **magnetic resonance imaging** (MRI), and is considered safe, using sound waves rather than radiation to generate an image.

Preparation

Little preparation is needed for the transvaginal ultrasound. A woman will need to undress from the waist down, and lie face-up on the examination surface. Legs may be put in stirrups, or a bolster may be placed under

KEY TERMS

Radiologist—A physician with special training in radiology, the study of x rays, Magnetic resonance imaging (MRI), ultrasound, and other imaging technology to assist in the diagnosis of a disease or condition.

False positive—A false positive is a positive finding of a test when, in fact, the true result was negative. This would mean that the test results indicate that a patient had a particular condition or disease when they do not.

QUESTIONS TO ASK THE DOCTOR

- What are you looking for with this test?
- Who will perform the test? Is that person board-certified?
- Who will read the results? Is that person board-certified?
- Does the facility utilize color flow Doppler imaging?
- When, how and from whom will I receive the results?
- If the result is positive, how will you evaluate if it was a false positive?
- Will my insurance cover the cost of this test?

the hips to tilt the pelvic area upwards to facilitate use of the probe, both for insertion as well as for the ultrasound process itself. The test is done with an empty bladder, which is more comfortable than the full bladder required for the abdominal ultrasound. This method may be a preferred choice for women who have difficulty with bladder control. A woman may wish to request that she insert the probe herself, which is similar to the insertion of a tampon. Gel that has been warmed will make insertion more comfortable.

Aftercare

Because of the small amount of gel used on the probe for easier insertion, a woman may wish to use a sanitary pad to protect her underpants from any minor leakage after she stands up. After the test a woman will be able to resume her regular scheduled activities.

Risks

The risk involved in using the transvaginal ultrasound is that of obtaining a false positive result, any resulting tests that would be ordered unnecessarily, and their accompanying emotional burden.

Normal results

The normal results of a transvaginal ultrasound are the finding of the normal shape and size of any structure evaluated, with no abnormal thickness, masses or growths of any kind found.

Abnormal results

Abnormal results include the finding of growths, such as masses or cysts, and any unexpected thickness of the structures evaluated. Because of the risk of false positive results, any abnormal findings should be further evaluated and confirmed before undergoing surgery or treatment for the suspected condition. Magnetic resonance imaging (MRI) is often ordered to further evaluate masses. An endometrial biopsy is performed to further evaluate a thickened uterine lining.

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Transverse myelitis

Description

Transverse myelitis (TM) is an inflammation or infection of the spinal cord in which the effect of the lesion spans the width of the entire spinal cord at a given level. The spinal cord consists of four regions: the

cervical (neck), followed by the thoracic (chest), the lumbar (lower back) and the sacral (lowest back). TM can occur in any of these regions. The disease is uncommon, but not rare, as it occurs in one to five persons per million population in any given year in the United States. It is equally diagnosed in both adults and children. TM may occur by itself or in conjunction with other illnesses such as viral or bacterial infectious diseases, autoimmune diseases such as multiple sclerosis, vascular illnesses such as thrombosis, and cancer.

The symptoms of TM depend on the level of spinal cord lesion with sensation usually diminished below the spinal cord level affected. Some patients experience tingling sensations or numbness in the legs with bladder control also being disturbed. The condition is usually diagnosed following **magnetic resonance imaging** (MRI) or **computed tomography** (CT) with "spinal taps" (lumbar punctures) taken for additional analysis. Recovery depends on the general health status of the patient and is usually considered unlikely if no improvement is observed within three months.

Causes

The exact cause of TM is unknown but research results point to autoimmune deficiencies, meaning that the patient's own immune system abnormally attacks the spinal cord, resulting in inflammation and tissue damage.

There is also evidence suggesting that TM occurs as a result of **spinal cord compression** by tumors or as a result of direct spinal cord invasion by infectious agents, especially the human immunodeficiency virus (HIV) and the human T-lymphotropic virus type I (HTLV-1).

TM is also listed among the spinal cord disorders occurring in patients diagnosed with AIDS.

Treatments

There is no specific treatment for transverse myelitis. Treatment of the illness is largely symptomatic, meaning that it depends on the specific symptoms of the patient. The region in which the spinal cord has been infected is critical but a course of intravenous steroids is generally prescribed at the onset of treatment.

Treatment of the bladder function impairment resulting from TM include drugs, external catheters for men and padding for women, with surgery recommended in certain cases. A common TM side effect is difficulty with stool evacuation and this condition can be treated by diets that include stool softeners and fiber.

As a result of TM, muscle groups below the affected level may become spastic. Treatment of spasticity usually involves prescriptions of drugs such as Baclofen (Lioresal), which stops reflex activity, and Dantrolene sodium (Dantrium) which acts directly on muscle. A new very well-tolerated drug, Tizanidine, has also recently been introduced in the United States. Muscle pain is generally treated with analgesics such as acetaminophen (Tylenol) or ibuprofen (Naprosyn, Aleve, Motrin). Nerve disorders might be treated with anticonvulsant drugs such as **carbamazepine**, **phenytoin** or **gabapentin** (Tegretol, Dilantin, Neurontin).

Alternative and complementary therapies

Individuals with TM may experience serious difficulty with common tasks such as dressing, bathing and eating. Complementary TM therapies may accordingly include a course of physical therapy so as to help patients recover mobility. This can be achieved with special exercises, canes, walkers and custom-designed braces.

KEY TERMS

Autoimmune disease—An illness which occurs when the body tissues are attacked by its own immune system. The immune system is a complex defense mechanism of the body whose primary function is to seek out and destroy invaders of the body, especially infections.

Catheter—A tubular, flexible instrument used to withdraw fluids from a body cavity, especially urine from the bladder.

Infectious disease—A disease caused by a virus or a bacterium. Examples of viruses causing an infectious disease are: HIV-1 virus, herpes simplex, cytomegalovirus, Epstein-Barr virus, leukemia virus. Examples of bacterial infectious diseases are: syphilis and tuberculosis.

Spinal cord—Elongated part of the central nervous system of vertebrates that lies in the vertebral canal and from which the spinal nerves emerge.

Spinal cord compression—A condition resulting from pressure being applied on the spinal cord, as from a tumor or spinal fracture. Depending on the location of the pressure, symptoms may include pain, numbness, tingling and prickling sensations as well as lock of sensory or motor functions.

Spinal tap—A diagnostic procedure by which a needle is introduced into the lower spine to collect cerebrospinal fluid for diagnostic testing.

After the acute phase, people with TM start the rehabilitation process. During this period, the focus of care is shifted from designing an effective TM treatment to learning to cope with a serious disease. TM patients must learn to cope with the loss of abilities which healthy people take for granted and this process is necessarily harder if TM is associated with AIDS or another serious autoimmune disease. Resources that may help this required adjustment are psychological assistance from counselors, relatives and friends, and making contact with TM support groups. The Transverse Myelitis Association may also be contacted: 3548 Tahoma Pl. West, Tacoma, WA 98466-2141 (info@myelitis.org; www.myelitis.org) Phone:253-565-8156.

See also Imaging studies; Lumbar puncture.

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Transverse Myelitis Association. 3548 Tahoma Pl. West, Tacoma, WA 98466-2141. (253) 565-8156. <http://www.myelitis.org>.

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Trastuzumab

Definition

Trastuzumab is a humanized monoclonal antibody produced by recombinant DNA technology that binds specifically to the human epidermal growth factor receptor 2 protein (also known as HER2 or neu or c-erb-2) that is found on the cell surface of some cancer tumors, most notably **breast cancer**. The drug is marketed in the United States under the Herceptin brand name.

Trastuzumab for potential treatment of gastric cancer is expected to commence during 2005 and a regulartory filing for this indication is due in 2008.

Purpose

Trastuzumab is a monoclonal antibody used to treat breast cancers that overexpress the HER2 protein, which occurs in about 25–30% of breast malignancies. By binding the HER2 protein on the tumor cell, the antibody targets it for destruction by the immune system. Based on data gathered in the laboratory, developers believe that trastuzumab triggers cell-mediated means to kill the tumor cells, through the action of natural killer cells and monocytes, two types of white blood cells. As binding of the antibody also slows growth of the tumor, it is theorized that the antibody may also block the interaction of the HER2 protein with a not yet identified growth factor that triggers rapid cell divisions.

Clinical trials have also begun or are soon to begin to test the use of trastuzumab against **osteosarcoma**, as well as endometrial, colorectal, kidney, pancreatic, prostate, ovarian, salivary gland, lung, and bladder cancers, as all of these tumor types can overexpress the HER2 protein on their surface.

Description

Trastuzumab is a genetically engineered monoclonal antibody. In 1998 it was approved by the FDA as a method of slowing growth of breast cancer tumors that overexpress the HER2 protein on the cell surface. Overexpression or overproduction of the HER2 protein is associated with aggressive disease and increased mortality.

Trastuzumab is approved for use either alone, or in combination with **paclitaxel**, a drug used for chemotherapeutic treatment of breast cancer. In clinical trials treating patients having breast cancer that has spread beyond the breast (metastatic breast cancer), trastuzumab had an overall response rate of 14%, with 2% having a complete response. When used in combination with paclitaxel treatment, the antibody reduced the risk of death by 24%. Higher expression of the HER2 protein on the tumor surface correlates with an increased chance of response to the drug. Additionally, clinical trials using trastuzumab in the TCH **chemotherapy** regime (Taxotere, **cisplatin** or **carboplatin**, and Herceptin) appears to avoid risk of heart problems (cardiotoxicity) seen with the paclitaxel/Herceptin combination.

Other clinical trials have begun testing the use of trastuzumab with other chemotherapy drugs such as **doxorubicin** (an antitumor anitbiotic), **cyclophosphamide** (an alkylating agent that interferes with mitosis and cell division), celecoxib (an aspirin-like drug called a cyclooxygenase-2, or COX-2, inhibitor), **capecitabine** (an antimetabolite that interferes with DNA and RNA growth), and others. Testing the combination of the monoclonal antibody and various cytokines, such as interleukins 2 and 12, is also ongoing. Additionally, doc-

KEY TERMS

Antibody—A protective protein made by the immune system in response to an antigen, also called an immunoglobulin.

Humanization—Fusing the constant and variable framework region of one or more human immunoglobulins with the binding region of an animal immunoglobulin, done to reduce human reaction against the fusion antibody.

IgG—Immunoglobulin type gamma, the most common type found in the blood and tissue fluids.

Interleukins—Cytokines responsible for the activation of B and T cells of the immune system.

Monoclonal—Genetically engineered antibodies specific for one antigen.

tors are also studying the combination of the antibody with other cancer treatments such as radiation and transplantation with peripheral stem cells.

Most of the trastuzumab sequence is derived from human sequences, while about 10% are from the mouse. The human sequences were derived from the constant domains of human IgG1 (called "constant" because it is essentially the same for all IgG antibodies) and the variable framework regions of a human antibody. These areas do not bind to the epidermal growth factor receptor 2. Using human sequences in this part of the antibody helps to reduce patient **immune response** to the antibody itself and is called humanization. The actual binding site of trastuzumab to the receptor is from a mouse anti-HER2 antibody.

Recommended dosage

Trastuzumab is administered intravenously, at a dose of 4 mg/kg for the initial administration, and 2 mg/kg for weekly maintenance until the disease progresses. The antibody can be given for longer periods to maintain tumor shrinkage.

Precautions

Extreme caution should be exercised when using trastuzumab to treat patients with existent heart problems. Also, patients with lung problems have an increased risk of side effects. Because the drug can pass to the fetus through the placenta and is present in breast milk, the drug should be used during pregnancy and nursing only if clearly indicated.

Side effects

The most severe side effects seen with this drug are heart and lung problems, which tend to occur most often in patients with a history of heart or lung disease. The use of anthracyclines and cyclophospamide in combination with trastuzumab also appears to increase these types of side effects.

The most common side effects with trastuzumab are infusion-associated symptoms, usually consisting of **fever** and chills on first infusion. The symptoms are often mild to moderate in severity and are treated with acetaminophen, **diphenhydramine**, and/or **meperidine**. Other common side effects include nausea and vomiting, and pain (in some cases at tumor sites), which occur less often after the first dose. Lowered red blood cell count (**anemia**), lowered white blood cell count (leukopenia), **diarrhea**, and infection occur more often in patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone. The severity of these symptoms usually do not result in discontinuation of therapy with Herceptin.

Other less common side effects are headache, abdominal pain, back pain, flu-like symptoms, sinusitis, rhinitis, pharyngitis, fluid retention (edema), insomnia, dizziness and **depression**.

Interactions

There have been no formal drug interaction studies done for trastuzumab. However, in clinical trials, this drug has a decreased clearance rate (time of removal from the body) when combined with some chemotherapeutic drugs including paclitaxel.

See also Monoclonal antibodies.

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Tretinoin

Definition

Tretinoin, a natural vitamin A metabolite, is an anticancer drug used in the treatment of acute promyelocytic leukemia (APL). Tretinoin is more commonly used to treat such skin disorders as acne, warts, hyperpigmentation, and reactions to sunlight.

Purpose

Tretinoin is given to APL patients with the goal of bringing on a remission. The drug is being investigated

as a treatment for skin cancer, and it is also available in an acne cream commonly called Retin-A.

As of 2004, tretinoin is also being investigated as a possible chemopreventive for breast cancer. The drug is thought to slow the spread of tumors and speed up the process of tumor cell self-destruction (apoptosis).

Description

Tretinoin causes abnormal leukemia cells in the blood to mature into normal cells (granulocytes). The exact mechanism of action is not known. In **clinical trials** 72–94% of APL patients experienced a complete remission when taking this drug. Tretinoin can be used to induce remission and to maintain remission.

Recommended dosage

The recommended dosage for adults with APL is 45 milligrams per square meter taken by mouth as two evenly divided doses. The physician will calculate the specific dose for each patient. The drug should be discontinued 30 days after remission or 90 days after treatment begins, whichever comes first.

Precautions

Patients who are hypersensitive to vitamin A or other retinoids should not take this drug. People should avoid tretinoin if they are sensitive to parabens, a preservative used in the drug's capsule. Pregnant or breastfeeding women should not take tretinoin. Women of childbearing age should take a pregnancy test to assure that they are not pregnant prior to starting this drug.

Side effects

Tretinoin has a number of side effects. Patients should discuss the risk of complications with their physician. Some side effects resemble symptoms that are common in APL patients. All side effects should be reported to a patient's doctor.

Side effects that are more commonly reported include headache, **fever**, dry skin and mucous membranes, **bone pain**, rash, **itching**, inflamed lips, sweating, nausea and vomiting, abdominal pain, **diarrhea**, constipation, indigestion, bloating, irregular heart beat, visual disturbances, earache, hair loss (alopecia), skin changes (including formation of inflammatory growths known as granulomas), vision changes, and bone inflammation.

Hemorrhage is a life-threatening complication. Blood coagulation studies are done while the patient is taking the drug to monitor the risk of hemorrhage. Hepatitis is another life-threatening side effect. Liver function tests can be abnormal in 50–60% of patients taking the drug. Liver function is monitored periodically while a person is taking the drug.

KEY TERMS

Leukocyte—White blood cell. Leukocytosis is the medical term for an excess number of white blood cells, and is seen in conditions such as infection and leukemia.

Metabolite—A product of metabolism.

Retinoid—Natural or artificial compound that is similar to vitamin A.

In addition, approximately one-quarter of patients taking tretinoin develop retinoic-acid-APL (RA-APL) syndrome. Symptoms include fever, weight gain, difficulty breathing, and other respiratory disorders. Some patients have cardiac changes and low blood pressure as part of this syndrome. The syndrome can occur two days after treatment begins or three to four weeks later. Symptoms must be reported to the patient's physician immediately so that treatment can begin. In rare cases this syndrome is fatal. Most patients do not need to stop taking tretinoin if the syndrome develops.

Approximately 40% of patients taking tretinoin develop high white blood cell counts (leukocytosis). If the number of white blood cells increases rapidly there is a higher chance of developing life-threatening complications. White blood cell counts are monitored during treatment. As many as 60% of patients taking tretinoin develop increased cholesterol and triglyceride levels. The levels drop when the medication is stopped. Cholesterol and triglyceride levels are monitored while the drug is being taken.

Tretinoin has other side effects that may impact the heart, skin, digestive tract, lungs, central nervous system, and other parts of the body. Patients should report all unusual symptoms to the doctor immediately.

Interactions

Tretinoin interacts with:

- Cimetidine (antipeptic ulcer drug)
- Cyclosporine (immunosuppressant)
- Dilitiazem (heart medication)
- Erythromycin (antibiotic)

- Glucocorticoids (steroids)
- Ketoconazole (antifungal drug)
- Phenobarbital (sedative/hypnotic)
- Pentobarbital (sedative/hypnotic)
- Rifampicin (an antituberculosis drug, also known as rifampin)
- Verapamil (heart medication)

See also Acute myelocytic leukemia; Antineoplastic agents.

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American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657-3000. <www.ashp.org>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

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Trichilemmal carcinoma

Definition

Trichilemmal carcinoma is an uncommon malignant tumor of the hair follicle, and is assumed to be the malignant counterpart of the benign trichilemmoma.

Description

Trichilemmal carcinomas most often occur on part of the skin that has been often exposed to the sun, like the face. The tumors look like tan or flesh-colored spots. They can resemble warts and sometimes have a hair in them. Usually, a trichilemmal carcinoma will occur as an isolated lesion.

Trichilemmal carcinomas are thought to be the malignant form of the non-cancerous tumors called trichilemmomas, which are seen in Cowden syndrome. Cowden syndrome is an inherited disorder that predisposes individuals to breast and **thyroid cancer**. The disease is inherited in an autosomal dominant inheritance pattern. With autosomal dominant inheritance, men and women are equally likely to inherit the syndrome. In addition, children of individuals with the disease are at 50% risk of inheriting it. **Genetic testing** is available for Cowden syndrome but, due to the complexity, genetic counseling should be considered before testing. Although they are thought to be related to trichilemmomas, none of the reports of trichilemmal carcinomas have been seen in patients with Cowden syndrome.

It is important to note that trichilemmal carcinoma is not the same as "malignant proliferating trichilemmal tumor," which is usually seen on the scalp and the back of the neck.

Demographics

Trichilemmal carcinomas are most often seen in older people. They occur with equal frequency in both males and females.

Causes and symptoms

The causes of trichilemmal carcinoma are unknown. The only recognizable symptom is the presence of an unusual, tan or flesh-colored spot on the skin.

Diagnosis

Diagnosis of a trichilemmal carcinoma is very important. Because the tumors are so rare, a physician may not immediately recognize its exact diagnosis. A dermatologist will suspect an abnormality on the skin

KEY TERMS

Metastasize—Cancer spreads to remote parts of body.

Pathologic examination—When a physician examines a small section of the tumor under a microscope.

and have it removed. It is only on the pathologic examination (when a physician examines the abnormality under a microscope) that the tumor can be correctly classified.

Treatment team

The treatment of trichilemmal carcinoma will involve a dermatologist (a physician who specializes in diseases of the skin) and a surgeon (a physician who will surgically remove the tumor).

Clinical staging, treatments, and prognosis

Once a trichilemmal carcinoma has been diagnosed, a surgeon must remove it. It is necessary that documented clear margins are obtained, indicating that the entire tumor has been removed. There is a chance that the tumor will recur (return) locally (in the same spot or near the same spot). If this occurs, the recurrent tumor needs to be surgically removed as well. It is very unlikely that a trichilemmal carcinoma will metastasize (spread to other parts of the body), and further treatment with **chemotherapy** is not needed.

Alternative and complementary therapies

Because trichilemmal carcinoma is easily treated with removal, there are no suggested alterative and/or complementary therapies.

Coping with cancer treatment

The surgical procedure to remove a trichilemmal carcinoma is relatively straightforward and low-risk. Most surgeries will be done on an outpatient basis, requiring no stay in the hospital. A small scar on the skin may be left after the tumor is removed.

Clinical trials

No **clinical trials** for trichilemmal carcinoma could be identified.

Prevention

Because the underlying cause of trichilemmal carcinoma is largely unknown, preventive strategies have not been suggested.

Resources

OTHER

Introduction of Skin Diseases. *Handbook of Dermatology and Venereology*. <http://www.hkmj.org.hk/skin/skintro.htm>.

Kristen Mahoney Shannon, M.S., C.G.C.

Trimethoprim *see* **Antibiotics**

Trimetrexate

Definition

Trimetrexate (Neutrexin) is a drug that was first used to treat bacterial infections, and is now being investigated as a treatment for several different cancers.

Purpose

Trimetrexate is most commonly used to treat **pneumonia** in patients with acquired immunodeficiency syndrome (AIDS). However, it was recently discovered that the drug was able to kill a variety of different cancer cells. As a result, trimetrexate is now considered to be an **investigational drug** for cancer treatment.

Ongoing **clinical trials** are using trimetrexate to treat a number of cancers including advanced colon and rectal cancers, advanced pancreatic cancer, and advanced squamous cell cancers of the head and neck. Results from many trials are still preliminary, but trimetrexate appears to be most promising as a treatment for advanced colon and rectal cancers.

Description

Trimetrexate glucoronate works by stopping cells from using **folic acid** (vitamin B9). As a result, cells cannot make essential components they need to survive, and they die. Because trimetrexate is toxic to both cancer cells and healthy cells, it is always used in combination with **leucovorin** (Wellcovorin, citrovorum factor). Leucovorin is a drug that protects healthy cells from the harmful effects of certain types of **chemotherapy**.

Trimetrexate can also enhance the anti-cancer effect of another chemotherapy drug called **fluorouracil** (Adrusil, 5-FU). Fluorouracil is frequently used to treat patients with colon and rectal cancers.

Recommended dosage

In clinical trials, patients with colon and rectal cancers were given trimetrexate, fluorouracil and leucovorin for 8-week cycles. A cycle consisted of six weeks of treatment followed by two weeks rest with no treatment. Patients received trimetrexate intravenously, with the dose depending on their weight. Twenty-four hours after trimetrexate treatment, patients received intravenous fluorouracil and leucovorin treatment. Some patients also took oral leucovorin every six hours for several days after their intravenous chemotherapy.

Patients with squamous cell cancer of the head and neck received trimetrexate in combination with **cisplatin** (Platinol), leucovorin and fluorouracil in a 21-day cycle. These patients also received surgery or **radiation therapy**. Pancreatic cancer patients received 8-week cycles of trimetrexate, fluorouracil and leucovorin, similar to that given to patients with **colon cancer**.

Precautions

Patients who are given oral leucovorin as part of their chemotherapy must take their medication. Trimetrexate is a toxic drug, and patients who do not take leucovorin may experience severe side effects. Pregnant women should not take trimetrexate because it may harm the fetus. Women who are taking trimetrexate should avoid becoming pregnant. In addition, women should not breast feed while taking this drug. The liver and kidney are used to break down and eliminate trimetrexate from the body. As a result, patients with a history of liver or kidney disease should tell their doctor.

Side effects

Patients taking trimetrexate will have their blood monitored regularly to check for the development of **myelosuppression**. Myelosuppression is a condition where a patient's bone marrow makes fewer blood cells and platelets than normal. As a result of this condition, patients have an increased risk of infection, may bleed more, and may experience symptoms of **anemia**. Trimetrexate may also cause damage to the kidneys and the liver. Some patients also experience **nausea and vomiting**, and may develop a rash or inflammation and sores in their mouths. Taking leucovorin with trimetrexate helps to reduce or eliminate the risk of experiencing many of these side effects.

KEY TERMS

Leucovorin—A drug used to protect healthy cells from toxic chemotherapy.

Myelosuppression—A condition where the bone marrow makes fewer blood cells and platelets than normal.

Interactions

Trimetrexate is known to interact with several other drugs. Some antifungal drugs such as ketoconazole (Nizoral) and fluconazole (Diflucan) interfere with the way the body breaks down trimetrexate. The antibiotic erythromycin also has this effect. Patients taking these drugs will be monitored carefully. The toxic effects of trimetrexate can be increased by other drugs. Patients should therefore tell their doctor about any medication they are taking whether it is prescription or over the counter.

Alison McTavish, M.S.

Triptorelin pamoate

Definition

Triptorelin pamoate is a synthetic luteinizing hormone-releasing hormone (LHRH) agonist, that is, a substance that reduces the level of sexual hormones in the system.

Purpose

Since its approval by the FDA (Food and Drug Administration) in June of 2000, triptorelin pamoate has been recognized as a successful option in the treatment of long-term cancer of the prostate gland. The prostate gland is a solid, chestnut-shaped organ surrounding the male urethra. It produces secretions that become part of seminal fluid. In the case of cancer of the prostate gland, it is advantageous to reduce prostate gland cell activity. One way to do this is to reduce the amount of hormones circulating in the system that will stimulate prostate activity. LHRH-agonists, such as triptorelin, are indicated when either **orchiectomy** (surgical removal of one of both testes) or the administration of the female hormone estrogen is either inadvisable or considered unacceptable by the person suffering from the cancer.

Triptorelin pamoate has been successfully used to alleviate symptoms in cases of such advanced **prostate cancer**, and is now being used and researched as a treatment for:

- all prostate cancers
- ovarian cancer
- *in vitro* fertilization
- endometriosis, or chronic disease of the mucous membrane lining the uterus
- uterine leiomyoma, also called uterine fibroids, a non-cancerous growth on the smooth muscle of the uterine wall
- precocious puberty, a condition in which children of either sex may undergo pubescent changes at an abnormally early age
- fibrocystic breast disease, or the presence of one or more benign tumors in the breast

Description

The human body provides balance in the provision of all chemicals necessary to its function. The pituitary gland and hypothalamus in the brain interact to release substances called gonadotropins, which trigger and regulate the production of estrogen (female) and androgen (male) hormones. Synthetic LHRH medications (similar in chemical makeup to natural LHRH enzymes) reduce the quantity of natural gonadotropins released. This reduces cell activity occurring in organs affected by these hormones, such as the prostate gland, ovaries, testes, uterus, and breasts, therefore slowing the growth of cancerous cells.

Triptorelin is a potent synthetic LHRH medication, effectively reducing gonadotropins if administered to maintain a continuous, therapeutic level in the body. Initially, there is often a temporary surge in circulating amounts of both male and female hormones, but usually within two to four weeks of beginning therapy, there is a marked reduction of these sex hormones. In men, there is a reduction in **testosterone** in the blood stream comparable to the level usually seen in surgically castrated men. Consequently, cells that rely upon these hormones for stimulation become less active. In most cases, the effect of triptorelin pamoate on sexual hormones is reversible once treatment is completed.

Recommended dosage

For advanced prostate cancer, the most common application for triptorelin, the usual dose is 3.75 milligrams (mg) given once per month as a single intramuscular injection. This will normally maintain a therapeutic level. If necessary, this medication may also be given intravenously.

KEY TERMS

Anaplastic—Poorly differentiated; immature and abnormal in function.

Benign tumor—A non-cancerous tumor that is incapable of invading surrounding tissue and spreading to other areas of the body.

Differentiated—Description of the similarity of function and appearance of cancer cells when compared to the normal, healthy tissue.

Exfoliative cytology—Evaluating cells that are shed from the body's surface.

Malignant tumor—A tumor that is capable of invading surrounding tissue and spreading to other areas of the body.

Pap smear—Analysis of cells found in vaginal secretions to determine the presence of uterine cancer. Also called a Pap test.

Pathologist—A doctor that examines cells under a microscope to determine the presence of the disease.

Pleomorphic—Irregular shape.

Tumor stage—An objective measurement gauging the cancer's progression.

Precautions

In the treatment of prostate cancer, there have been reported flare-ups of the disease at the onset of therapy. Patients with a prostate tumor affecting the spinal cord or urinary flow should use caution, as an increase in tumor activity may initially worsen symptoms. Triptorelin pamoate is capable of causing harm to fetuses if administered to pregnant women. During long-term treatment of endometriosis or uterine fibroids, bone loss has been reported.

Side effects

The following side effects have either been reported or were observed:

- nausea and vomiting
- hot flashes
- vaginal dryness
- impotence

- loss of sex drive
- breakthrough bleeding
- sleep disturbance
- diarrhea
- fatigue
- hair loss (alopecia)
- mouth sores
- breast tenderness
- weight gain
- pain at injection site
- increases in cholesterol
- headache

Interactions

Because triptorelin pamoate has only had FDA approval since June of 2000, not all information in known regarding its interactions with other medicines. Currently, no drug interactions have been reported.

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Tumor grading

Definition

Tumor grading is an estimate of the tumor's malignancy and aggressiveness based on how the tumor cells appear under a microscope and the number of malignant characteristics they possess.

Purpose

Tumor grading, together with the stage of the tumor, assists doctors in planning treatment strategies. Although grading is an important part of describing most cancers, it is extremely important in helping to determine the course of treatment for specific cancers such as soft tissue **sarcomas**, brain tumors, lymphomas, breast and **prostate cancer**. Generally higher grade and higher stage tumors require more drastic therapy than lower grade and stage tumors. Tumor grade and stage also help doctors give an estimation of the prognosis of the patient. Patients with lower grade and stage tumors usually have a more positive prognosis than patients with higher grade and stage tumors. Patients should thoroughly discuss the grade and stage of their tumor with their physician, asking about necessary treatments and prognosis.

KEY TERMS

Dialysis—A medical procedure that uses a special machine to filter waste products from the blood and restore it. It is a life-sustaining procedure in end-stage kidney failure.

Electrolytes—Substances or particles that dissolve into ions, (atoms with a positive or negative charge) such as potassium or sodium, and carry water molecules across cell membranes, regulating electric charge in order to maintain the proper oxygen flow of body fluids.

Metabolic—Pertaining to the physical and chemical process of synthesis and breakdown of substances necessary to sustain life.

Nephrology—The study of the kidneys—their structure and function.

pH—A measure of the alkalinity or acidity of a substance.

Description

Before a tumor can be assigned a grade, a sample of tissue must be removed for microscopic evaluation. Tissue samples can be obtained through one of various types of **biopsy** or through exfoliative **cytology** (e.g. Pap smear). A pathologist analyzes various characteristics of the tissue. Some characteristics include the size and shape of the nucleus; the ratio of the volume of the nucleus to the volume of the cytoplasm; the relative number of dividing cells called the mitotic index; the organization of the tissue; the boundary of the tumor; and how well-differentiated the cells appear—how close to normal the cells seem in maturity and function.

Benign tumors have normal-looking cells. That is, they have small and regular shaped nuclei, small nuclear volume relative to the rest of the cellular volume, a relatively low number of dividing cells, normal and well-differentiated tissue that has a well-defined tumor boundary. However, malignant tumors generally have all or several of the following characteristics: large and pleomorphic (irregular-shaped) nuclei, large nuclear volume compared to the rest of the cellular volume, a high number of dividing cells, disorganized and anaplastic (poorly differentiated) tissue that has a poorly defined tumor boundary.

Depending on the number of malignant characteristics present, the **American Joint Commission on Cancer** has recommended that the tumor be given a grade using G0 through G4.

QUESTIONS TO ASK THE DOCTOR

- What are the microscopic characteristics this cancer presents?
- What grade is this cancer?
- What courses of treatment do you recommend for this grade of this type of cancer?

- G1 Well-differentiated (Low-grade and less aggressive)
- G2 Moderately well-differentiated (Intermediate-grade and moderately aggressive)
- G3 Poorly differentiated (High-grade and moderately aggressive)
- G4 Undifferentiated (High-grade and aggressive)

Alternatively, Roman numerals I through IV may be used. Low-grade tumors are assigned lower Roman numerals (e.g. grade I), indicating that the tumor is less aggressive. High-grade tumors are assigned higher Roman numerals (e.g. grade IV), indicating that the tumor is very aggressive, growing and spreading quickly.

- I Well-differentiated (Low-grade and less aggressive)
- II Moderately well-differentiated (Intermediate-grade and moderately aggressive)
- III Poorly differentiated (High-grade and moderately aggressive)
- IV Undifferentiated (High-grade and aggressive)

There are some cancers that have their own grading convention. For example, the Gleason system is a unique grading system that was developed to describe adenocarcinoma of the prostate. Pathologists analyze prostate tissue and give a Gleason score ranging from 2 to 10, subject to the number of malignant characteristics observed. Well-differentiated, less aggressive prostate tumors with only a few malignant characteristics are given lower Gleason numbers, while inadequately differentiated, more aggressive prostate tumors that possess many malignant characteristics are assigned higher Gleason numbers.

See also Tumor staging.

Resources

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Tumor lysis syndrome

Description

Tumor lysis syndrome is a life-threatening metabolic emergency frequently associated with certain types of tumors (neoplasms). Concentrations of intracellular electrolytes, those that are within the cell, differ from extracellular electrolytes, or those that are outside the cell and in the bloodstream. In tumor lysis syndrome, tumor cells lyse, or break apart, releasing their contents into the blood stream. The result is a dangerous alteration in the normal balance of serum electrolytes—potassium, phosphate and uric acid levels are elevated, while calcium levels are decreased. The changes occur so quickly and can be so dramatic, that immediate death can result.

Causes

Many factors contribute to the development of tumor lysis syndrome. Most of the research performed to date revolves around high-grade non-Hodgkin's **lymphoma** cases, 40% of which demonstrate laboratory evidence of tumor lysis syndrome. (An estimated 6% demonstrate clinical evidence of the syndrome.) Tumors that carry the highest risk of the development of tumor lysis syndrome are those that are large and bulky, usually greater than eight to ten cm (3-4 in.), and comprised of rapidly dividing cells. In addition, tumors that respond well to treatment are associated with tumor lysis syndrome because treatment results in rupture of a large number of cells.

Most often, the syndrome is associated with blood-based (hematologic) tumors, such as non-Hodgkin's lymphoma, particularly **Burkitt's lymphoma**, and **acute leukemia**. Though less likely because of lower rates of cell division, tumor lysis syndrome can also occur in solid tumors such as **breast cancer**. The Washington Manual of Medical Therapeutics associates the following cancer types with tumor lysis syndrome:

- Non-Hodgkin's lymphoma (NHL)
- Acute lymphocytic leukemia (ALL)
- Acute myelocytic leukemia (AML)
- Chronic lymphocytic leukemia (CLL)
- Chronic myelocytic leukemia (CML)
- Breast cancer
- Testicular cancer
- Medulloblastoma
- **Merkel cell carcinoma**
- Neuroblastoma
- Small cell **carcinoma** of the lung

Usually, tumor lysis syndrome develops after the administration of combination **chemotherapy** regimens, but it may also occur spontaneously or as a result of radiation or corticosteroid therapy. Lactic acid dehydrogenase (LDH) is an enzyme found in cells of body tissues. An increase in the LDH level is considered a marker of bulky disease that correlates with the risk of tumor lysis syndrome.

Patients with underlying kidney (renal) dysfunction and/or decreased urine output are at a higher risk of developing tumor lysis syndrome. Without optimal kidney functioning, waste products that build up cannot be excreted in the urine at a high enough rate. Patients with cancer may be predisposed to conditions that increase the risk of renal failure due to increased uric acid buildup. For example, a patient undergoing chemotherapy may experience **nausea and vomiting**, and may, as a result, be dehydrated, increasing the risk. The same patient may have decreased white blood cell counts, making him or her more susceptible to infections. Many **antibiotics** adversely affect the kidneys, also increasing the risk.

Treatments

Treatment is aimed at prevention and supportive care, with the main goals being to prevent renal failure and severe electrolyte imbalances. Patients at risk receive treatment on an inpatient basis to allow for close monitoring by medical personnel. At all times, patients should have reliable intravenous access. Prior to initiating treatment, a patient's hydration status and electrolyte levels are carefully evaluated. If there are abnormalities, a treatment delay may be considered, though this is not always an option.

Laboratory tests are done frequently to monitor levels of calcium, potassium, phosphate, magnesium and uric acid. A typical hospital protocol may require blood be drawn for these tests every two to six hours over the course of two to three days. Following are prevention and management strategies for each of the major electrolyte imbalances, hyperuricemia, hyperkalenia, hyperphosphatemia, and hypocalcemia.

Hyperuricemia is a medical term used to describe an abnormal increase of uric acid levels in the blood that can lead to acute renal failure. There are several methods employed to prevent kidney damage—aggressive hydration being a major focus. Intravenous (IV) hydration is started before treatment and continues throughout to maintain a urine output of 100 to 200 milliliters per hour (ml/hr). Medications called diuretics, such as furosemide or acetazolamide, are given to help increase urine output when necessary.

Urine may be alkalized to prevent uric acid buildup. Alkalization can be accomplished by adding sodium bicarbonate to the patient's IV fluid. For example, the basic maintenance IV fluid may consist of 5% dextrose in 0.25 normal saline, to which sodium bicarbonate, in amounts ranging from 50 to 200 milliequivalents (mEq—the total number of charges of electrolytes in solution), may be added. Urine pH is routinely tested, and the sodium bicarbonate is periodically increased or decreased to maintain a pH level between 7 and 8.

Urine alkalinization is somewhat controversial. If urine is too alkaline, calcium phosphate crystal formation may occur, increasing the likelihood of renal failure. However, it is generally believed that if urine output levels are appropriately maintained, calcium phosphate will be diluted, and the possibility of crystal formation will diminish.

Patients at risk for tumor lysis syndrome may also be given **allopurinol** prophylactically. One dose of 600 milligrams (mg) may be given the day before treatment, followed by 300 mg once a day for the remainder of treatment days. Allopurinol is effective because it inhibits the formation of uric acid. In 2004, a new drug called rasburicase became available in the United States. It prevents the damaging effects of tumor lysis syndrome with fewer side effects.

Hyperkalemia is a medical term used to describe an abnormal increase of potassium levels in the blood that can cause dangerous abnormalities in heart rhythms, heart attack, and muscle weakness. Frequent monitoring with electrocardiography (EKG) is recommended in patients at risk for tumor lysis syndrome so that alterations in the electrical activity of the heart can be caught early. Potassium-rich foods may also be restricted to prevent already elevated levels from increasing. Sometimes, medications such as Kayexalate are administered to help reduce potassium levels.

Hyperphosphatemia is a medical term used to describe an abnormal increase on phosphate levels in the blood that can cause neuromuscular irritability and worsen kidney function. Malignant cells may contain up to four times as much phosphate as non-malignant cells. Patients experiencing acute tumor lysis syndrome may be instructed to reduce their dietary intake of phosphate. In addition, they may be given medications that bind to phosphate, thereby inhibiting its absorption in the intestines.

Hypocalcemia is a medical term used to describe an abnormal decrease in calcium levels in the blood that can cause muscle spasms (tetany), muscle cramps, and seizures. A calcium supplement may be required.

Dialysis is a procedure used to normalize electrolyte imbalances through the diffusion and ultrafiltration of

KEY TERMS

AFP (Alpha-fetoprotein)—A tumor marker associated with liver, testicular, and ovarian cancer.

Beta-HCG (Beta-human chorionic gonadotropin)—A tumor marker associated with testicular cancer and tumors, such as choriocarcinoma and molar pregnancies, that begin in placental cells called trophoblasts.

Biopsy—The process of taking a sample of tumor tissue through a needle.

CA 15-3 (Cancer antigen 15-3)—A tumor marker associated with breast cancer.

CA 19-9 (Cancer antigen 19-9)—A tumor marker associated with pancreatic cancer.

CA 27-29 (Breast carcinoma-associated antigen)—A tumor marker associated with breast cancer.

CA 125 (Cancer antigen 125)—A tumor marker associated with ovarian cancer.

CEA (Carcinoembryonic antigen)—A tumor marker associated with many cancers, especially liver, intestinal, and pancreatic.

Prognosis—The predicted outcome of a disease.

PSA (Prostate specific antigen)—A tumor marker associated with prostate cancer.

Sensitivity—A test's ability to detect all cases of a disease.

Serial measurements—A series of measurements looking for an increase or decrease over time.

Specificity—A test's ability to detect only the disease in question.

Tumor markers—Biochemicals produced by tumor cells or by the body in response to tumor cells. Their levels in the blood help evaluate people for certain kinds of cancer.

fluid. Potassium, for example, can be separated and filtered from fluid, bringing levels back to a safer range. Hemodialysis is a procedure that removes waste products through the blood. Dialysis can alternatively be performed through the peritoneum, the tissue that lines the abdominal area and surrounds the organs in what is called peritoneal dialysis. Because peritoneal dialysis does not clear phosphate and urate as efficiently, and because it is not feasible in patients with abdominal tumors, hemodialysis is the preferred method. A doctor who specializes in nephrology will generally examine a high-risk patient before cancer treatment begins, to prepare for the possibility of dialysis treatment. In some cases, dialysis is started as a preventive measure, either before or during chemotherapy treatment.

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Tumor markers

Definition

Tumor markers are measurable biochemicals that are associated with a malignancy. They are either produced by tumor cells (tumor-derived) or by the body in response to tumor cells (tumor-associated). They are typically substances that are released into the circulation and thus measured in the blood. There are a few exceptions to this, such as tissue-bound receptors that must be measured in a **biopsy** from the solid tumor or proteins that are secreted into the urine.

Purpose

Though tumor markers are rarely specific enough to be used alone to diagnose cancer, they do have a number of clinical uses. They can be used to stage cancer, to indicate a prognosis, to monitor treatment, or in follow-up to watch for cancer recurrence. Changes in some tumor markers have been sensitive enough to be used as targets in **clinical trials**. When used for diagnosis, tumor markers are used in conjunction with other clinical parameters such as biopsy and radiological findings. Although there are a multitude of tumor markers, very few of them have found their way into clinical practice because of their lack of specificity. However, some of

these non-specific markers have found a place in monitoring cancer treatment rather than in diagnosis.

Description

As tumor cells grow and multiply, some of their substances can increase and leak into the bloodstream or other fluids. Depending upon the tumor marker, it can be measured in blood, urine, stool or tissue. Some widely used tumor markers include: AFP, beta-HCG, CA 15-3, CA 19-9, CA 27.29, CA 125, CEA, and PSA. Some tumor markers are associated with many types of cancer; others, with as few as one. Some tumor markers are always elevated in specific cancers; most are less predictable. However, no tumor marker is specific for cancer and most are found in low levels in healthy persons, or can be associated with non-neoplastic diseases as well as cancer. Also, no tumor marker test is free of false negatives or false positives.

Once cancer is diagnosed, tumor marker levels sometimes help to determine the extent of cancer. Higher levels can indicate more advanced cancer and a worse prognosis in some cases. The patient and their physician may use this information to choose between more or less aggressive treatments.

Monitoring cancer treatment is the most common use of tumor markers. As cancer is reduced, levels often decrease. Stable or increasing levels often indicate that the cancer is not responding to treatment. The choice of tumor marker to use for monitoring is important. Only a marker elevated before treatment should be used to monitor a person during or after treatment. Timing of the tests is also important. Each tumor marker has a unique life span in the blood. To monitor a treatment's success, enough time must have passed for the initial marker to be cleared from the blood. Tests done too soon may be falsely elevated because the marker produced by the untreated cancer is still present.

Watching for cancer recurrence after treatment is another reason for tumor marker testing. Periodic testing can sometimes detect a recurrence often months earlier than could an ultrasound, x ray, or physical examination.

Tumor marker tests are performed in a lab using immunological techniques. A sample of blood or other tissue is mixed with a substance containing specific antibodies to each tumor marker. If that tumor marker is present, these very specific antibodies bind to the markers. Some type of label, often a radioactive substance, is then used to measure the amount of bound marker and antibody. From this measurement, the amount of tumor marker is calculated. The results are usually available within a few days.

Conclusions based on tumor marker tests are seldom based on one test result but on a series of test results, called serial measurements. A series of increasing or decreasing values is more significant than a single value.

Tumor marker testing is currently the object of much research and attention. Their use is directed by approval from the Food and Drug Administration (FDA) and guidelines established by organizations such as the American Society of Clinical Oncology and the American Cancer Society. Not all tumor receptor marker tests are widely available nor are they widely accepted.

Oncofetal antigens

There are two common oncofetal antigens, alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA). Carcinoembryonic antigen CA 72-4 is a more recently discovered oncofetal antigen just coming into usage. The oncofetal antigens are so named because they are normally produced during embryonic development and decrease soon after birth. Cancer cells tend to dedifferentiate, or revert to a more immature tissue and begin to produce fetal antigens again. Oncofetal antigens are very non-specific and expressed by a wide number of cancer types. However, they are used both to monitor a patient's progress and their response to treatment over time.

ALPHA-FETOPROTEIN (AFP) Elevated AFP typically indicates a primary liver tumor or a germ cell tumor of the ovary or testicle. AFP is a glycoprotein produced in high amounts by fetal tissue and is elevated during pregnancy. It is most widely used as a marker for hepatocellular **carcinoma** and **testicular cancer** but is also associated with **ovarian cancer**. Seventy percent of people with liver cancer have increased AFP levels. In China, where liver cancer rates are high, AFP is used as a **screening test** for that disease. AFP levels indicate the extent of cancer, and serial measurements are used to monitor treatment response. Non-cancerous liver conditions such as cirrhosis and hepatitis have moderately increased levels of AFP.

CARCINOEMBRYONIC ANTIGEN (CEA) CEA is a glycoprotein most often associated with colorectal cancer, and used to monitor patients with this type of cancer. Its most popular use is in early detection of relapse in individuals already treated for colorectal cancer. After surgery, serial measurements indicate the surgery's success and are used to detect early signs of recurrence. It has recently been found to be useful when measured during surgery for colorectal cancer to help determine prognosis and who will benefit from adjuvant treatment.

CEA is measured in the blood plasma. It is very non-specific and can be increased in many types of cancer: gastrointestinal, colorectal, ovarian, bladder, cervical, stomach, kidney, lung, pancreatic, liver, prostate, thyroid, **melanoma**, **lymphoma**, and breast. People with

noncancerous conditions, such as cirrhosis or peptic disease, or inflammatory intestinal conditions such as colitis or diverticulitis, may also have increased levels. CEA levels can be elevated in elderly patients and in those who smoke.

CANCER ANTIGEN 72-4 (CA 72-4) The more recently identified carcinoembryonic protein is CA 72-4. Although it is slightly elevated with most carcinomas, it is mostly associated with gastric carcinoma (stomach cancer). CA 74-2 is finding a role in the management of patients with gastric carcinoma.

Cancer antigen 15-3 (CA 15-3)

CA 15-3 is produced by cells in the breast and increased levels can be associated with **breast cancer**. Rarely increased in women with early breast cancer, it may be used to detect recurrence of cancer in women following treatment or **mastectomy** and to monitor treatment for women with advanced breast cancer. However, **adenocarcinomas** of the ovary, lung, colon, and pancreas also express elevated CA 15-3 levels. Non-cancerous conditions sometimes associated with elevated CA 15-3 include benign breast or ovarian disease, endometriosis, pelvic inflammatory disease, and hepatitis. Pregnancy and lactation are also related to high CA 15-3 levels.

Cancer antigen 27-29 (CA 27-29)

CA 27-29, also called breast carcinoma-associated antigen, is used as a marker for breast cancer. Eighty percent of women with breast cancer have an increased CA 27-29 level. This marker may be used with other procedures and tumor marker levels such as CA 15-3 to check for recurrences of cancer in previously treated women. Serial measurements monitor treatment response and identify recurrence.

Levels of CA 27-29 may also be increased in cancers of the colon, stomach, kidney, lung, ovary, pancreas, uterus, and liver. Noncancerous conditions associated with elevated CA 27-29 include first trimester pregnancy, endometriosis, ovarian cysts, non-cancerous breast disease, kidney disease, and liver disease.

HER-2/neu

HER-2/neu is an oncogenic growth factor receptor also known as c-erbB-2. It is measured in the tissue from a biopsy either by immunological assays of the protein or polymerase chain reaction (PCR) to identify the DNA. The presence of HER-2/neu is generally associated with a poorer prognosis for breast cancer. It can also help to determine treatment options, since newer drugs can block this protein and decrease cancer growth. The most widely known of these drugs is **trastuzumab** (brand name Herceptin).

Estrogen receptor

Measurement of the estrogen receptor (ER)is used specifically to evaluate breast cancers. It gives an indication of prognosis and responsiveness to therapy. Tissue from a biopsy is used to measure the estrogen receptor. Most breast cancers in post-menopausal women are ER-positive, meaning that they require estrogen to grow. These ER positive breast cancers are less aggressive than ER negative breast cancers, which are found generally in pre-menopausal women.

Cancer antigen 125 (CA 125)

Although produced by a number of cell types, CA 125 is primarily produced by ovarian cancer cells. Eighty percent of women with ovarian cancer have increased CA 125 levels. Although the test is not sensitive or specific enough to be used for screening, it contributes to a diagnosis when combined with an ultrasound and pelvic examination. Blood levels of CA 125 are used primarily to monitor the treatment of ovarian cancer. A falling CA 125 level usually indicates that cancer is responding to the treatment. After diagnosis and treatment, serial measurements help detect remaining or recurrent cancer. A negative or normal result, however, does not guarantee the absence of cancer.

Women may have increased CA 125 levels during menstruation and pregnancy. Increased levels are also found in pelvic inflammatory disease, endometriosis, pancreatitis, and liver disease. Elevated levels are also associated with non-ovarian cancers including cancers of the uterus, cervix, pancreas, liver, colon, breast, lung, or digestive tract.

Prostate specific antigen (PSA)

Prostate specific antigen (PSA) levels, along with the digital rectal examination, are used to screen for **prostate cancer**. PSA is a protein produced by the prostate gland and can be overproduced in prostate cancer. It is perhaps the best tumor marker in use because of its tissue specificity, meaning that it is produced only by the prostate. Men over the age of 50 years are advised to consider annual screening for prostate cancer. Men at high risk for prostate cancer, such as African Americans or those with a family history of the disease, should begin screening at age 40. Once a diagnosis of prostate cancer is made, PSA levels can help determine the stage of the cancer, monitor the response to treatment, and watch for recurrence.

Measurements of PSA following **prostatectomy** are useful in determining the success of surgery. Any PSA level following surgery would indicate residual prostate tissue, possibly from **metastasis**. PSA levels can also be used to detect a recurrence of prostate cancer. PSA is also increased in benign prostatic hyperplasia (BPH), an enlarged prostate condition common in older men.

PSA can be found in the serum in two states, bound and free. Measuring both PSA levels can provide more specificity to the test and reduce unnecessary biopsies. The percentage of free PSA is greater in BPH than prostate cancer. If the total PSA level is higher than 4.0 nanogram/milliliter (ng/mL) and the free PSA level is less than 25%, a prostate biopsy is indicated.

PSA levels may increase after ejaculation. Men are recommended to abstain from sexual intercourse or masturbation for 48 hours before the test. PSA levels may also increase after prostate manipulation following the digital rectal exam.

Prostatic acid phosphatase (PAP) originally found to be produced by the prostate and thought to be a marker for prostate cancer. It is now found to be elevated with testicular cancer, leukemia, non-Hodgkin's lymphoma and several noncancerous conditions.

Cancer antigen 19-9 (CA 19-9)

CA 19-9 has been identified in patients with digestive tract or intra-abdominal carcinomas such as colorectal cancer, pancreatic cancer, **stomach cancer** and **bile duct cancer**. In pancreatic cancer, higher levels are associated with more advanced disease. After diagnosis, levels help predict the success of surgery and monitor the course of the cancer. Not all people with pancreatic cancer have increased CA 19-9 levels. This antigen is related to the Lewis blood group and so only patients positive for the Lewis blood group antigen will test positive for CA 19-9. It is also increased in liver and **gastrointestinal cancers** and in noncancerous diseases, including pancreatitis, gallstones and jaundice.

Human chorionic gonadotropin (hCG)

Human chorionic gonadotropin is normally produced by the placenta during pregnancy. There are two protein subunits that make up HCG, beta and alpha. It is the beta subunit that is increased in women's serum during early pregnancy. It is also the beta subunit that is increased in some malignant tumors. Tumors that secrete beta-hCG are typically **germ cell tumors** such as teratocarcinomas. These are tumors found in the ovaries and testes that contain embryonal tissue. Rarely, these types of tumors are found in the pineal region of the brain where beta-hCG can serve as a marker. Levels of hCG rise with choriocarcinoma and with trophoblastic disease, a rare cancer that develops from an abnormally fertilized egg. **Gestational trophoblastic tumors** also secrete AFP and this test is often used in combination.

HCG is most often used to screen for cancer of the testis or ovary. Serial measurements monitor the progress and treatment of these cancers. This marker can be elevated in individuals who use **marijuana**.

Squamous cell carcinoma (SCC) Antigen

Squamous cell carcinoma (SCC) antigen was first identified in **cervical cancer**. It is a marker for squamous cell cancers, which can occur in the cervix, head and neck, lung, and skin. Levels of SCC can be used as an aid to stage the carcinoma and to determine the response to treatment.

Bence-Jones protein

Patients with plasmacytomas such as **myeloma** overproduce monoclonal immunoglobulins, also called M proteins. The Bence-Jones protein refers to the immunoglobulin light chain, a portion of these immunoglobulins. The Bence-Jones protein is secreted into the urine where it can be measured. It was the first tumor marker identified.

Neuron-specific enolase (NSE)

NSE is a protein found mainly in neurons and neuroendocrine cells. It is elevated in tumors derived from these tissues, including **neuroblastoma** and small cell lung cancer. It can give information about the extent of the disease, the patient's prognosis and the patient's response to treatment. NSE can also be elevated in medullary thyroid cancers, carcinoid tumors, pancreatic endocrine tumors, and melanoma.

Hormone assays

Tumors of the endocrine glands oversecrete their corresponding hormones. By measuring particular hormones, clues can be obtained regarding certain cancers. For instance, breast cancer cells may secrete prolactin and estrogen. Medullary carcinoma can secrete **calcitonin**. Pheochromocytomas secrete catecholamines. Tumors of the pituitary gland may secrete growth hormone or cortisol. Carcinoid tumors secrete serotonin. Some tumors of the pancreas secrete insulin. Serial measurements can also monitor treatment for these tumors.

Enzymes

Several serum enzymes can be measured to help detect metastases in cancer patients. Tumors that

metastasize to the liver cause increases in serum alkaline phosphatase, gamma-glutamyltransferase, and transaminases. Although these are not necessarily tumor markers, they indicate liver damage that may be caused by metastatic cancer. Tumors that metastasize to the bone sometimes secrete elevated alkaline phosphatase. Lactate dehydrogenase is an enzyme found throughout the body. Because of this it cannot be used as a marker for cancer. It can, however, be used to monitor the treatment of some types of cancer including germ cell tumors, testicular cancer, **Ewing's sarcoma**, non-Hodgkins lymphoma and some types of leukemia.

Precautions

There is not a good consensus in the medical community about the value of most tumor markers. Because they lack specificity and accuracy, their use is limited. False positives can cause emotional distress and fear. It is not yet determined if there is a savings of life or money with testing. Currently, much controversy surrounds the issue of mass screening for cancer using tumor markers.

Preparation

Tumor marker tests usually require 5-10 mL of blood. A healthcare worker ties a tourniquet on the patient's upper arm, locates a vein in the inner elbow region, and inserts a needle into that vein. Vacuum action draws the blood through the needle into an attached tube. Collection of the sample takes a few minutes and results are available within a few days.

Some markers, such as those for **bladder cancer**, **multiple myeloma**, and plasmacytomas, are measured in the urine. Typically this requires a 24-hour urine sample, which means that the individual must collect all of his or her urine for 24 hours. This is usually about 1.5 quarts or more. These results are then available within a few days.

Other tumor markers require tissue samples for analysis. These include **receptor analysis** such as estrogen receptor and Her-2/neu. Tissue samples are obtained by biopsy. This is usually done by inserting a needle through the skin and into the tumor. The area is typically numbed prior to the procedure. These results are also available within two to three days.

Aftercare

Discomfort or bruising may occur at the puncture site or the person may feel dizzy or faint. Pressure to the puncture site until the bleeding stops reduces bruising. Warm packs to the puncture site relieve discomfort.

KEY TERMS

Cachexia—A side effect of cancer therapy characterized by weight loss due to lack of appetite and wasting away due to malnutrition.

Cytokines—Molecules released by cells to regulate the length and intensity of an immune response and to mediate intercellular communication.

Macrophage—A type of white blood cell that produces antibodies and molecules for cell-to-cell immune responses.

Regional perfusion—Forcing a liquid through the blood at the capillary beds at or near a specific site.

There is a rare chance of infection occurring especially after biopsy. Any sign of infections should be watched for such as pain and redness.

Normal results

- AFP: 99% of (nonpregnant) people have less than 15 ng/mL; 95% have less than 6 ng/mL. Serum AFP levels higher than 400 micrograms/L are associated with cancer or some other pathology.
- Beta-HCG: in males, less than 2.5 IU/L; in females, less than 5.0 IU/L; in postmenopausal females, less than 9.0 IU/L.
- CA 15-3: less than 40 U/mL.
- CA 19-9: less than 40 U/mL.
- CA 27.29: less than or equal to 38 U/mL.
- CA 125: less than 35 U/L.
- CEA: less than or equal to 5 ng/mL.
- PSA: less than 4 ng/mL; PSA levels increase with age. Age-specific values range from 2.0 micrograms/L at age 40 to 7.2 micrograms/L at age 80. Typically, levels below 4.0 micrograms/L rule out prostate cancer.

Abnormal results

The meaning of an increased tumor marker level depends on the specific marker, the person's medical history, and why the test was done. Knowledge of the patient's history and additional tests and physical examinations are needed to correctly interpret tumor marker test results.

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA, 30329. (800) 227-2345. <http://www.cancer.org>.

American Society of Clinical Oncology. 225 Reinekers Lane, Suite 650, Alexandria, VA 22314. (703) 299-0150. <http://www.asco.org>.

National Cancer Institute. 9000 Rockville Pike, Building 31, Bethesda, MD 20892. (800) 4-CANCER. <http://www.nci.nih.gov>.

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Tumor necrosis factor

Definition

Tumor necrosis factor is a protein produced by several of the body's cell types, such as white blood cells, red blood cells, and other cells that line the blood vessels. It promotes the destruction of some types of cancer cells.

Description

In the 1970s, researchers took sarcoma cells in culture and exposed them to a protein produced by white blood cells. The protein caused necrosis (death) of the sarcoma cells but had little effect on normal cells in the culture. Hence, the protein was called "tumor necrosis factor" (TNF).

TNF is a type of cytokine released by white blood cells. Cytokines are a group of molecules that are released by many different cells to communicate with other cells and regulate the duration of an **immune response**. There are many different kinds of cytokines, each with a different effect on specific target cells. Once a cell releases the cytokines, they bind to corresponding receptors located on target cells, thus causing a change to take place within the target cell. Tumor necrosis factor is released by special white blood cells called macrophages. Although researchers are still investigating the exact mechanism by which TNF kills cancer cells, it is clear that TNF binds to receptors located on the surface of cancer cells, causing a change and then death of the cell. This was found to be true in animal models. As a result, researchers thought TNF might enhance the reaction of the human immune system to cancer cells.

In the mid-1980s, TNF became available in recombinant form and was analyzed in clinical human trials. At that time, researchers discovered that TNF administered systemically was toxic to humans' normal tissues at the maximum doses required to kill all of the cancer cells, thus limiting its usefulness. At maximum doses required to kill cancer cells, patients experienced **fever**, loss of appetite (anorexia), and cachexia (severe **weight loss**, malnutrition, and wasting away of the body).

However, TNF can be effectively combined with other systemic chemotherapeutic drugs such as **doxorubicin** and **etoposide**. TNF in conjunction with the above drugs enhances DNA breakage in tumor cells, contributing to their death. In addition to administering TNF systemically, TNF (with or without other chemotherapeutic drugs) can be forced through the blood at the capillary beds at or near the site of the tumor. The regional perfusion of TNF allows larger dosages to be administered only in the area requiring the treatment. Therefore, less

KEY TERMS

Disseminated disease—The presence of widespread malignancy implying a stage of IV.

Malignancy—A general term for cancers of all tissue types, sarcomas, and leukemias.

Metastasis—The spread of malignancy to another site within the body. To regional lymph nodes: regional metastasis. To distant sites: distant metastasis.

Prognosis—The expected outcome

Systemic disease—Disease that is widely metastatic or present throughout the body.

normal and healthy tissue is disrupted before reaching the maximum tolerable limits. Research performed in 1998 (by Lejeune, et al.) found regional perfusion to be especially successful in the case of **melanoma metastasis**, resulting in complete remission of 70% to 80% of patients.

Although TNF is valuable in killing cells in melanoma and sarcoma tumors, it can promote growth of other kinds of cancers. Therefore, the action of TNF is continually under research with the hope of increasing its effectiveness on killing cancer cells, while decreasing the toxic side effects on healthy tissue.

Sally C. McFarlane-Parrott

Tumor staging

Definition

Tumor staging is the process of defining at what point in the natural history of the malignant disease the patient is when the diagnosis is made. The organ and cell type in which the malignancy has developed defines the type of malignancy. For example, adenocarcinoma of the lung defines that the cancer originated in the mucus-secreting cells lining the airways of the lung. Staging is different than defining the type of cancer; it is the process of defining the degree of advancement of the specific type of malignancy in the patient at the time of presentation (the time when the diagnosis is made). Because there are many different types of malignancy arising from many different organs in body, the specifics of staging systems vary.

Purpose

Staging fulfills an organizational role that is central to treatment of cancer. After the tumor is staged, the treatment team knows to what degree the cancer has evolved in its natural history. This knowledge will provide the information necessary to formulate a plan of treatment and will allow an estimate of the success of that treatment (prognosis). Finally, by establishing uniform criteria for staging, people with the same type of malignancy presenting at the same stage can be treated equivalently. If a new treatment is tested that improves the long-term prognosis then that treatment will become the new standard of care. Thus, staging is vital to the processes of research and scientific reporting.

Prognosis

The first question that most patients want answered when they find they have cancer is "How am I going to do?" They want to know the ultimate outcome—their prognosis. Because of the existing research on the natural history, or progression, of the disease, this information is available on a statistical basis. Staging, then, helps define the patient's prognosis. Intuitively, one would think that those presenting with an earlier stage have a better prognosis. For the most part, that is correct.

Scientific reporting and research

When a patient develops a life-threatening disease such as cancer, the physicians and other members of the treatment team intervene in an effort to improve the prognosis. Treatment regimens are defined as good or bad based on how they influence the prognosis of the disease. Staging allows medical professionals to interpret whether or not their efforts are favorably influencing the natural history of the disease. Once a patient's cancer stage has been established, a baseline exists against which to measure the efficacy of the cancer treatment that follows for that patient.

Staging plays a similar "baseline" role when considering a large group of cancer patients. In order to gauge accurately the effectiveness of any cancer treatment, researchers must know if the patients' conditions really are comparable. If they are, comparisons between treatments are fair. If the patients' conditions vary at the outeset of a study, then comparing the outcomes of different treatments is not useful.

Staging provides that useful, objective standard so that researchers can accurately compare specific treatments in certain stages of particular cancers. Staging

allows uniformity in treatment protocol and reporting of the data related to outcome. As new treatment protocols are developed, they can be tested on patients with the same type and stage of cancer and the two groups compared. If there is improvement with a new treatment protocol, that treatment regimen will be adopted as standard. Physicians can use these established best practices to determine treatments for their patients.

Criteria for staging

As it became apparent to medical professionals that staging of malignancies was necessary for accurate assessment of treatment regimens and defining the treatment recommendations themselves, criteria for staging needed to be developed. Initially this was done for individual tumors separately. Because of the need for uniformity, a universal set of criteria was desired. The TNM system of staging has been adopted for the most part for this reason. It has been developed and updated by The American Joint Committee on Cancer (AJCC). Some of the types of malignancy do not fit well into the TNM criteria and others have older systems that are still in use because they are effective and are deeply established in scientific literature.

TNM system

This system of staging is the general format used for staging cancer of all types and is updated and maintained by the AJCC. The "T" stands for tumor size. The "N" stands for spread to lymph nodes, (nodal **metastasis**). The "M" stands for metastasis, (spread of the cancer to sites in the body other than the organ of origin. When the diagnosis of cancer is made, the physical examination along with laboratory testing and **imaging studies** will be performed to define the TNM status of the patient. The TNM status will define stage.

The tumor size, "T" will be assessed by physical examination or various imaging modalities depending on the accessibility of the tumor. The "T" value is generally defined as 1 through 4 on the basis of size and whether or not the tumor is invading structures that surround it. In cancer so early that it is felt to be incapable of spreading, it is assigned a "T" value of 0. The "T" value is, in essence, a description of the tumor in its local place of origin. As time passes and the staging system is updated, the "T" value is being subdivided in certain types of cancer. The subdivisions are indicated by letters "a" through "d" and also have a graduated value system. For example: T1 **breast cancer** is a tumor sized 2 cm or less in greatest dimension. T1a is less than 0.5 cm, T1b is 0.5 to 1.0 cm, and T1c is 1.0 to 2.0 cm.

In many cancers, there seems to be a progression from the place of primary origin, then to the regional lymph nodes, and then throughout the body. Lymph nodes can be thought of as filters that drain tissue fluid coming from a particular organ. If that organ has developed a cancer and some of the cells flow away with the tissue fluid to the lymph node filter that is draining that organ, the cancer may begin to grow there also. Assessment of lymph node involvement thus becomes the next step in staging and defines the "N" value. Since the word metastasis means that the cancer has spread from its point of origin to somewhere else in the body and the lymph nodes are in the region, the "N" value defines presence of regional metastasis. The assessment is performed by physical examination and imaging studies of the region involved. "N" is assigned a value of 0 for no nodes involved, or depending on the anatomic nature of the region, values 1 through 3.

"M" stands for distant metastasis. As mentioned previously, metastasis is the spread of the primary tumor to elsewhere in the body. When that spread or metastasis is outside the region of the primary tumor, the patient has distant metastasis. The "M" value is assessed by physical exam, laboratory studies, and imaging studies. Different cancers have different typical patterns of metastasis. Common areas of metastatic involvement are lung, liver, bone, and brain. The "M" value is assigned either 0 or 1. Another term used to describe the patient who has distant metastasis is that of having systemic disease. In the TNM system virtually all patients with an "M" value of 1 have stage IV disease. The "M" value may also have a subscript defining the organ of metastatic involvement.

After the values for TNM have been determined as accurately as possible, the values are grouped together and a stage value is assigned. The stage value is usually I through IV, (and is written in roman numerals). Each stage may be subdivided, (A,B,C...), if it is useful for treatment recommendations and reporting. In general, stage I implies the tumor is confined to its source of origin and stage IV implies distant metastasis or systemic disease. Because of different anatomical, prognostic, and treatment considerations, the intermediate stages are defined by different tumor sizes, the presence or absence of local invasion of the tumor into surrounding structure, or the number and/or presence of involved lymph nodes. Treatment recommendations and expected outcome are both defined to a large extent by stage. The specific criteria for each stage are contained in the *AJCC Cancer Staging Manual*.

An example of TNM staging follows. This example is the staging criteria for non-small-cell lung cancer.

- Stage 0: A small group of cancerous cells have been found in one location in the lung.

- Stage I: The cancer is only in the lung and has not spread anywhere else.
- Stage II: The cancer has spread to nearby lymph nodes.
- Stage III: The cancer has spread to more distant lymph nodes, and/or other parts of the chest like the diaphragm.
- Stage IV: The cancer has spread to other parts of the body (distant metastasis).

Special staging systems

In the development of staging systems it has been recognized that some malignancies do not fit well into the scheme of the TNM system or that the system in place reflects the same information as the TNM system. Thus there are a few special staging systems in use for specific organs of involvement. The goal is the same for these schema as for TNM; to define the point in the natural history at presentation, to allow establishment of prognosis and treatment recommendations, and to facilitate scientific research and reporting.

COLON CANCER: DUKE'S STAGING The Duke's staging system is similar to the TNM system when describing colo-rectal cancer. This was the original staging system for colon and rectal cancers; however, the TNM staging sytem has begun to replace the Duke's system for colon and rectal cancers.

OVARIAN CANCER: FIGO SYSTEM FIGO stands for the International Federation of Gynecology and Obstetrics. This organization developed staging criteria for the various gynecologic malignancies and the one for cancer of the ovary is still used somewhat though the TNM criteria are gradually replacing the FIGO system. In the FIGO system, **ovarian cancer** is staged I through IV similar to the TNM scheme then each stage is subdivided into A, B, or C, depending on defined criteria.

LYMPHOMA: ANN-ARBOR STAGING Anatomically, the lymph system and its nodes are found throughout the body. Malignancies involving the lymph system (lymphomas), do not fit the typical TNM scheme well. The Ann Arbor staging criteria are instead utilized to classify this group of malignancies. The goals of the Ann Arbor **lymphoma** staging system are to define the degree of advancement of the disease so that treatment recommendations can be made and prognosis can be estimated, and to facilitate consistent reporting and research.

The Ann Arbor system classifies lymphoma into four stages based on anatomic lymph nodal group involvement. Disease confined to one nodal group or location defines stage I. Disease limited to one side of the diaphragm, (the muscle separating the chest from the abdomen), defines stage II. Stage III patients have disease on both sides of the diaphragm and stage IV patients once again have disseminated disease. Consideration of involvement of the liver, spleen, and bone marrow are also considered in this system. Finally, the stage is subdivided into categories of A and B depending on the presence of symptoms of **itching**, **weight loss**, **fever**, and **night sweats**. Those having symptoms receive the designation "B" and have a worse prognosis.

LEUKEMIA: THE FAB AND RAI/BINET STAGING SYSTEMS Leukemia is the type of malignancy that begins in the cells of the marrow that produce the cellular components of blood, the progenitor cells. These malignancies are truly systemic from their outset and do not fit any form of the TNM system. Still there is need to categorize the presenting features of the patients with these diseases to help make treatment recommendations, estimate prognosis, and to facilitate scientific research and reporting. The acute leukemias are staged by the FAB (French, American, British) system, and **chronic lymphocytic leukemia** is classified by the Rai/Binet system.

LUNG CANCER, SMALL CELL Unlike other types of lung cancer, the staging of small cell lung cancer is relatively simple. This is because approximately 70% of patients already have metastatic disease when they are diagnosed, and small differences in the amount of tumor found in the lungs do not change the prognosis. Small cell lung cancer is usually divided into three stages:

- Limited stage: The cancer is found only in one lung and in lymph nodes close to the lung.
- Extensive stage: The cancer has spread beyond the lungs to other parts of the body.
- Recurrent stage: The cancer has returned following treatment.

Defining the stage

The process of defining stage is quite simple. First, the diagnosis is established by study of the patient and by tissue **biopsy**. Once the cell type and organ of origin are established, the staging criteria are reviewed. The patient will undergo a series of diagnostic tests to define the various parameters of the staging criteria. The results of these tests define the extent of the disease and establish the stage. The known typical natural history of the disease dictates the types of testing done. The tests differ for each type of malignancy.

Special concerns

Clinical vs. pathological stage

The stage of the patient's disease may be categorized into clinical or pathological. As mentioned, the

known natural history of the disease and the staging criteria are utilized to define the stage of the patient at the time of presentation. The investigations performed often involve an initial degree of uncertainty when they are based on clinical grounds alone. For example, the physical exam or the imaging of a particular group of lymph nodes may show that they are enlarged but the enlargement may not accurately define whether they are truly involved with cancer. This issue may only be resolved by removing some or all of the suspect enlarged nodes, sometimes by biopsy before treatment or sometimes by the removal of the questionable nodes at the time of definitive treatment. The evaluation under the microscope of the clinically enlarged nodes will define whether they are really involved with cancer or merely enlarged. When staging criteria are based on clinical assessment alone, it is referred to as the clinical stage. Once the results of the microcopic evaluation are known the true stage or pathologic stage may be assigned.

Stage is uniform and accurate

One of the main goals of staging is to facilitate communication so that like patients are compared to like patients. It is imperative that the adopted staging criteria are rigidly adhered to or inaccurate comparisons may be made and the results of research to develop better treatment regimens will be difficult to interpret.

Tumor grade

When the tissue obtained for diagnosis is evaluated under the microscope for cell type, often another index called grade is defined. As the pathologist analyzes the malignant cells, attention will be given to how close to a normal cell the malignant cells appear to be. If they are very similar, the malignant cells are not felt to be too aggressive and a low grade value is assigned. The more atypical the malignant cells appear to be, the more aggressive the tumor is and a higher grade value is assigned. Grade is usually assigned a value of I through IV though more levels can be assigned depending on the particular cancer.

The estimate of grade is just that—an estimation. It is subjective in nature and cannot be determined quantitatively. Though useful in predicting prognosis, the correlation is not exact. Rather, grade is included as only one of the factors influencing prognosis. Grade may be included as part of the actual staging criteria; however, it usually is not part of the scheme.

Tumor boards

A tumor board is a body of specialists in the treatment of cancer that convenes to discuss the aspects of patients presenting with cancer. The AJCC encourages the development of tumor boards throughout the nation to facilitate the use of staging and reporting of cancer statistics from region to region throughout the country. In addition to allowing the collection of vital cancer statistics, local tumor boards create a forum where the clinical aspects of a patient's cancer may be discussed to provide recommendations or to play a role in education.

See also Tumor grading; Individual cancer entries for specific staging information for each cancer.

Resources

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Abelhoff, Armitage, and Niederhuber Lichter. *Clinical Oncology Library*. Philadelphia: Churchill Livingstone 1999.

Richard A. McCartney, M.D.

Tumor suppressor genes *see* **Cancer genetics**

U

Ultrasonography

Definition

Ultrasonography is the study of internal organs or blood vessels using high-frequency sound waves. The actual test is called an ultrasound scan or sonogram. Duplex ultrasonography uses Doppler technology to study blood cells moving through major veins and arteries. There are several types of ultrasound. Each is used in diagnosing specific parts of the body.

Purpose

An ultrasound is a noninvasive, safe method of examining a patient's eyes, pelvic or abdominal organs, breast, heart, or arteries and veins. It is often used to diagnosis disease, locate the source of pain, or look for stones in the kidney or gallbladder. Ultrasound produces images in real time. Images appear on the screen instantly. It may also be used to guide doctors who are performing a needle **biopsy** to locate a mass. (Needle biopsies are often used to obtain a sample of breast tissue to test for cancer cells.) Duplex/Doppler ultrasound aids in diagnosing a blockage in or a malformation of the vessel. Different color flows aid in identifying problem areas in smaller vessels. Endoscopic ultrasound combines a visual endoscopic exam, during which a flexible tube called an endoscope is threaded down the throat, with an ultrasound test. The ultrasound probe is attached to the end of the endoscope. An endoscopic ultrasound is helpful in determining how deeply a tumor has grown into normal tissues or the gastrointestinal tract. During a transvaginal ultrasound, the ultrasound probe is inserted into the vagina to obtain better images of the ovaries and uterus. Color flow Doppler imaging, using a transvaginal probe, is being performed to detect abnormal blood flow patterns associated with **ovarian cancer**.

Precautions

Ultrasound is considered safe with no known risks or precautions. The exam uses no radiation. Under normal circumstances the exam is normally painless. However, if the patient has a full bladder, pressure exerted during the exam may feel uncomfortable. An ultrasound conducted in conjunction with an invasive exam carries the same risks as the invasive exam.

Description

The patient will be asked to lie still on an exam table in a darkened room. The darkness helps the technician see images on a screen, which is similar to a computer monitor. Sometimes the patients are positioned so they can watch the screen. The technician will apply a lubricating gel to the skin over the area to be studied. Ultrasound uses high-frequency sound waves to produce an image. A small wand-like device called a transducer produces sound waves that are sent into the body when the device is pressed against the skin. The gel helps transmit the sound waves, which do not travel through the air. Neither the patient nor the technician can hear the sound waves. The technician moves the device across the skin in the area to be studied. The sound waves bounce off the fluids and tissues inside the body. The transducer picks up the return echo and records any changes in the pitch or direction of the sound. The image is immediately visible on the screen. The technician may print a still picture of any significant images for later review by the radiologist.

Preparation

Depending on the type of ultrasound ordered, patients may not need to do anything prior to the test. Other ultrasound studies may require that the patient not eat or drink anything for up to 12 hours prior to the exam, in order to decrease the amount of gas in the bowel. Intestinal gas may interfere in obtaining accurate results. The patient must have a full bladder for some exams and an empty bladder for others.

KEY TERMS

Biopsy—Removal of a tissue sample for examination under a microscope to check for cancer cells.

Endoscopy—Examination of the upper gastrointestinal tract using a thin, flexible instrument called an endoscope.

Radiologist—Doctor who has received special training and is experienced in performing and analyzing ultrasounds and other radiology exams.

QUESTIONS TO ASK THE DOCTOR

- Did you see any abnormalities?
- What future care will I need?

Aftercare

Remove any gel still left on the skin. No other aftercare is required following an ultrasound.

Risks

Standard, diagnostic ultrasound is considered risk-free. Risks may be associated with invasive tests conducted at the same time, such as an endoscopic ultrasound or an ultrasound-guided needle biopsy.

Normal results

An ultrasound scan is considered normal when the image depicts normally shaped organs or normal blood flow.

Abnormal results

Abnormal echo patterns may represent a condition requiring treatment. Any masses, tumors, enlarged organs or blockages in the blood vessel are considered abnormal. Additional testing may be ordered.

Resources

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Debra Wood, R.N.

Upper gastrointestinal endoscopy

Definition

Upper gastrointestinal endoscopy is a procedure that allows the doctor to visually examine the upper portions of the gastrointestinal tract, using a flexible tool called an endoscope. The endoscope has a light source and projects an image on a video screen. An endoscope may also be used to assist with other diagnostic exams and procedures. For instance, an ultrasound probe can be placed on the end of the endoscope to evaluate how deeply a tumor has penetrated the esophagus or wall of the stomach. An endoscope may be used to assist with placement of a permanent feeding tube or to treat a bleeding ulcer.

Purpose

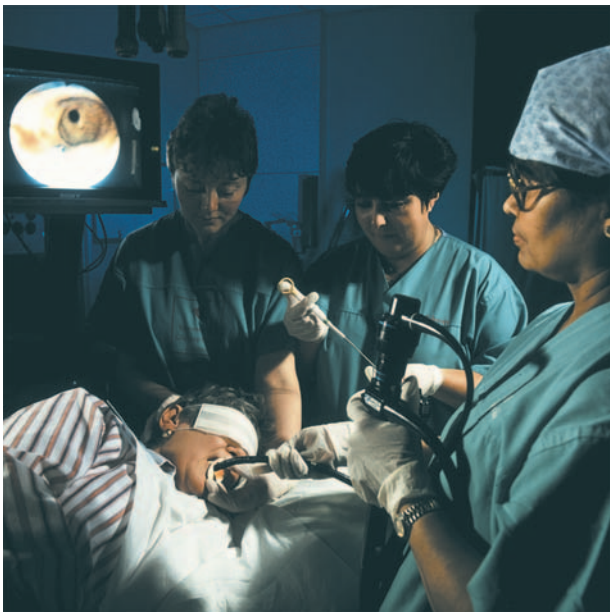
An upper gastrointestinal endoscopy aids in the investigation of the source of pain, difficulty swallowing, bleeding or other symptoms of an upper abdominal problem. During an endoscopy the doctor can obtain samples of tissue for **biopsy**, to check for the presence of cancer cells or the bacteria responsible for most stomach ulcers. Various instruments can be passed through the endoscope to treat problems, such as controlling bleeding due to an ulcer. The procedure may be performed on patients who have had stomach surgery to assess for cancer or the return of an ulcer. It may also be used to monitor patients at high risk for upper **gastrointestinal cancers**.

Precautions

Patients with a history of heart and lung disease and those with blood-clotting problems require special precautions. For instance, a patient with artificial heart valves or a history of infection of the lining of the heart will need **antibiotics** to prevent infection. Patients with an intestinal perforation, or puncture in the gastrointestinal tract, should not have an upper gastrointestinal endoscopy. Patients must be able to cooperate during the procedure. Those who are not able to cooperate are not good candidates for an endoscopy.

Description

An endoscopy may take place in the physician's office or in a hospital. An intravenous (IV) line will be started in a vein in the arm. Through the IV line, the patient generally receives a sedative and a pain-killer if needed. The medication will help the patient feel relaxed and drowsy. A local anesthetic is usually sprayed into the throat to prevent a gag reflex. Dentures are removed.



Doctors performing an endoscopy examination of a woman's stomach and taking a biopsy. The endoscope has been inserted through the patient's mouth and fed down her throat. The image obtained by the endoscope is on the screen at upper left. *(Copyright Deep Light Productions, Science Source/Photo Researchers, Inc. Photo reproduced by permission.)*

KEY TERMS

Biopsy—Removal of a tissue sample for examination under a microscope to check for cancer cells.

Duodenum—The first portion of the small intestine.

Endoscope—A thin, flexible, lighted tube that is passed down the throat and enables the doctor to view the esophagus, stomach lining and duodenum.

Perforation—Puncture or tear.

Staging—Determination of how advanced the cancer is.

Ultrasound—The study of internal organs using high-frequency sound waves.

A mouthpiece will help to keep the mouth open. Patients are positioned onto their sides. The doctor slowly advances the lubricated endoscope down the throat, into the stomach. Air will be passed through the endoscope to make it easier for the doctor to see the lining of the gastrointestinal tract. The endoscope will be repositioned to see different parts of the stomach and the small intestine. The exam usually takes less than an hour. The patient is able to breathe independently during the exam. In some cases a biopsy may be taken. Biopsy forceps or a brush used to secure cells are passed through the endoscope. The tissue sample is taken and then removed through the endoscope.

Preparation

The doctor should be informed of any allergies as well as all the medications that the patient is currently taking. The doctor may instruct the patient not to take certain medications, like aspirin and anti-inflammatory drugs that interfere with clotting, for a period of time prior to the procedure. The patient should not eat or drink anything for at least eight hours prior to the endoscopy. The doctor should be informed if the patient has had heart valves replaced or a history of an inflammation of the inside lining of the heart, so that appropriate antibiotics can be administered to prevent any chance of infection. Risks and benefits of the procedure will be explained to the patient. The patient will be asked to sign a consent form.

Aftercare

The patient will be monitored for an hour or two after the procedure, while the effects of the medication wear off. Due to the sedative, the patients will need to arrange for someone to drive them home after the procedure.

Patients may feel bloated due to the air that is introduced into the stomach during the procedure, and may have a sore throat for a couple of days. Patient should contact the doctor if they develop difficulty swallowing, chest pain, severe abdominal pain, throat soreness that becomes more severe or rectal bleeding.

Risks

Endoscopy is usually considered safe when performed by a specially trained physician. As with any invasive procedure it is not risk-free. Complications include bleeding and perforation (puncturing a hole in the lining of the gastrointestinal tract). Scopes are cleaned and disinfected between patients so any risk of transmitting infectious disease from one patient to another by the endoscope would be negligible.

Normal results

A pale reddish pink lining with no abnormal-looking masses or ulcerations is considered a normal result.

QUESTIONS TO ASK THE DOCTOR

- Did you see any abnormalities?
- How soon will you know the results of the biopsy (if one was done)?
- When can I resume any medications that were stopped?
- What future care will I need?
- Which problems should prompt me to call you?

Abnormal results

Evidence of an ulcer or other lesion would be considered an abnormal result. If the biopsy determines the presence of cancer cells, a diagnosis of cancer is made. The appearance of the lesion, including its size or if there are multiple lesions, often helps with staging and treatment plans. An ultrasound probe attached to the endoscope also may help with staging.

Resources

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Debra Wood, R.N.

Upper GI series

Definition

An upper GI examination is a fluoroscopic examination (a type of x-ray imaging) of the upper gastrointestinal tract, including the esophagus, stomach, and upper small intestine (duodenum).

Purpose

An upper GI series is frequently requested when a patient experiences unexplained symptoms of abdominal pain, difficulty in swallowing (dysphagia), regurgitation, **diarrhea**, or **weight loss**. It is used to help diagnose disorders and diseases of, or related to, the upper gastrointestinal tract, including cases of hiatal hernia, diverticuli, ulcers, tumors, obstruction, **enteritis**, gastroesophageal reflux disease, Crohn's disease, and pulmonary aspiration.

Precautions

Because of the risks of radiation exposure to the fetus, pregnant women are advised to avoid this procedure. Patients with an obstruction or perforation in their bowel should not ingest barium (a radioactive substance used to show contrast in the images) for an upper GI, but may still be able to undergo the procedure if a water-soluble contrast medium is substituted for the barium.

Glucagon, a medication sometimes given prior to an upper GI procedure, may cause nausea and dizziness.

Description

An upper GI series takes place in a hospital or clinic setting and is performed by an x-ray technician and a radiologist. A radiologist typically is in attendance to oversee the procedure and view and interpret the fluoroscopic pictures. Before the test begins, the patient is sometimes administered an injection of glucagon, a medication which slows stomach and bowel activity, to allow the radiologist to get a clearer picture of the gastrointestinal tract. In order to further improve the clarity of the upper GI pictures, the patient may be given a cup of baking soda crystals to swallow, which distend the stomach by producing gas.

Once these preparatory steps are complete, the patient stands against an upright x-ray table, and a fluoroscopic screen is placed in front of him. The patient will be asked to drink from a cup of flavored barium sulfate, a thick and chalky-tasting liquid that allows the radiologist to see the digestive tract, while the radiologist views the esophagus, stomach, and duodenum on the fluoroscopic screen. The patient will be asked to change positions frequently in order to coat the entire surface of the gastrointestinal tract with barium. The technician or radiologist may press on the patient's abdomen in order to spread the barium. The x-ray table will also be moved several times throughout the procedure. The radiologist will ask the patient to hold his breath periodically while exposures are being taken. The entire procedure may take up to 45 minutes.

In some cases, in addition to the standard upper GI series, a doctor may request a detailed intestine, or small

KEY TERMS

Dysphagia—An inability to swallow, or difficulty with swallowing.

Fluoroscopy—Also called radioscopy, this procedure involves the examination of internal body structures using x-rays and projecting images on a fluorescent screen.

Necrosis—Death of cells in a body tissue.

Radiologist—A doctor who specializes in an area of medicine that focuses on the use of radiation to diagnose and treat disease.

QUESTIONS TO ASK THE DOCTOR

- What is the purpose of this examination?
- When will I know the results?
- How will I be notified of the results?
- How will the examination results help to determine the next step in management of my condition?
- What are the alternatives to this diagnostic exam?

bowel, radiography and fluoroscopy series; it is also called a small bowel follow-through (SBFT). Once the preliminary upper GI series is complete, the patient will be escorted to a waiting area while the barium travels down the rest of the small intestinal path. Every 15 to 30 minutes, the patient will return to the x-ray suite for additional x rays. Once the barium has traveled down the small bowel tract, the test is complete. This procedure can take anywhere from one to four hours.

Esophageal radiography, also called a barium esophagram or a barium swallow, is a study of the esophagus only, and is usually performed as part of the upper GI series. It is commonly used to diagnose the cause of difficulty in swallowing (dysphagia) and for detecting hiatal hernia. A barium sulfate liquid, and sometimes pieces of food covered in barium or a barium tablet, are given to the patient to drink and eat while a radiologist examines the swallowing mechanism on a fluoroscopic screen. The test takes approximately 30 minutes.

Preparation

Patients must not eat, drink, or smoke for eight hours prior to undergoing an upper GI examination. Longer dietary restrictions may be required, depending on the type and diagnostic purpose of the test. Patients undergoing a small bowel follow-through exam may be asked to take **laxatives** the day prior to the test. Upper GI patients are typically required to wear a hospital gown, or similar attire, and to remove all jewelry, so the camera has an unobstructed view of the abdomen. Patients who are severely ill may not be able to tolerate the procedure.

Aftercare

No special aftercare treatment or regimen is required for an upper GI series. The patient may eat and drink as soon as the test is completed. The barium sulfate may make the patient's stool white for several days, and patients are encouraged to drink plenty of fluids in order to eliminate it from their system.

Risks

Because the upper GI series is an x-ray procedure, it does involve minor exposure to ionizing radiation. Unless the patient is pregnant, or multiple radiological or fluoroscopic studies are required, the small dose of radiation incurred during a single procedure poses little risk. However, multiple studies requiring fluoroscopic exposure that are conducted in a short time period have been known, on rare occasions, to cause skin death (necrosis) in some individuals. This risk can be minimized by careful monitoring and documentation of cumulative radiation doses administered to these patients.

Another risk is barium impaction, which occurs when the patient is unable to completely expel the barium contrast agent before it eventually dries and hardens. The risk of barium impaction is greatest in elderly patients and those with colon obstruction or colon motility disorder.

Normal results

A normal upper GI series will show a healthy, functioning, and unobstructed digestive tract.

Abnormal results

Obstructions or inflammation, including ulcers of the esophagus, stomach, or small intestine, or irregularities in the swallowing mechanism are some of the possible abnormalities that may show up on an upper GI series. Other abnormalities may include polyps, foreign bodies, or congenital anomalies. Upper GI series are helpful in the diagnosis of gastric (stomach) cancer.

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Paula Anne Ford-Martin

Upper gastrointestinal series *see* **Upper GI series**

Urethral cancer

Definition

A rare form of cancer that can affect both men and women, urethral cancer is a type of cancer that develops in a person's urethra.

Description

The urethra is the tube in a person's body that empties urine from the bladder. In women, the urethra is a very short tube that opens to the outside of the body just above the vagina, whereas in men it is a much longer tube that goes through the prostate gland and penis to the outside of the body.

In both men and women, urethral cancer has a tendency to invade local and adjacent soft tissues. By the time of diagnosis, the majority of tumors are locally advanced, which sometimes results in a poor prognosis despite aggressive treatment. Urethral cancer rarely metastasizes (spreads) to distant locations. In women, the most common sites of tumor invasion are the vagina and bladder, whereas in men, tumor invasion most commonly occurs in the deep tissues of the perineum, the prostate, and the penile and scrotal skin. Most of the urethral tumors, in both men and women, are the squamous-cell type. The second most common type is transitional-cell **carcinoma**.

Demographics

Because urethral cancer is so rare (approximately 600 cases a year), there is not much data validating the best methods of treatment. Generally speaking, urethral cancer is found more often in women than in men. Although people of many different ages have been diagnosed with urethral cancer, it is usually found in people over the age 50. Urethral cancer is more common in white people than in black people; however, blacks tend to have a worse prognosis after urethral cancer has been diagnosed.

Causes and symptoms

Patients with a history of **bladder cancer** have an increased risk of urethral cancer. Although cigarette smoking and exposure to certain chemicals, such as the ones that used to be used in the rubber industry, can contribute to the development of bladder cancer, the same correlation does not exist with urethral cancer. Certain types of human papillomavirus are suspected as the cause of urethral cancer in some people, although in many cases the cause is unknown.

Often the first symptom of urethral cancer is blood in the urine, although it may be present in such small amounts that it can only be detected in a microscope. Sometimes, however, the urine may be visibly red. There may be pelvic pain and the flow of urine may be obstructed, making it difficult to urinate. A lump may be present on the urethra. In women, tiny growths that bleed may be present at the external opening of the urethra.

Diagnosis

To diagnose urethral cancer, a physician will examine the patient physically for any lumps. A urinalysis may also be done to check for the microscopic presence of blood and to check for infection. Patients may need to have a **cystoscopy**, which will allow the physician to see inside the urethra. In adults, the procedure is usually done under local anesthesia, which means that the area around the urethral opening is injected with an anesthetic. The cystoscope, which is a long, flexible tube made of plastic or metal, is inserted through the urethra. The tube has a lens and a fiberoptic light that allows the physician to examine the area through a scope. It may be necessary to take a small sample of the tissue, which is referred to as a **biopsy**. The sample will then be viewed under a microscope to check for any signs of cancer.

Treatment team

The treatment team is comprised of physicians from a variety of medical specialties. For example, a patient

diagnosed with urethral cancer may have a treatment team that includes the patient's primary care physician and urologist, as well as a radiologist, oncologist, surgeon, and **pain management** specialist. Women may also seek the advice of their gynecologist. At home caretakers are also part of the treatment team, providing important physical and emotional support to the patient. Physicians and patients that value a holistic approach to fighting cancer may add a variety of other advisors to the treatment team, such as psychologists, pastors, and alternative medicine specialists.

Clinical staging, treatments, and prognosis

After a diagnosis of cancer has been made, patients will need to have more tests to determine if the cancer has spread to other areas of the body. The treatment is gauged depending on the stage of the disease. The stage of urethra cancer is determined by the cancer's location and whether it has metastasized. According to the National Cancer Institute, the following are used to describe the different stages of urethral cancer:

- Anterior urethral cancer: the cancer is located on the urethra near the outside of the body
- Posterior urethral cancer: the cancer is located on the urethra near the bladder
- Urethral cancer associated with invasive bladder cancer: the cancer has spread to the urethra because of the presence of bladder cancer

Surgery, **radiation therapy**, and **chemotherapy** are the conventions treatment options for urethral cancer. According to the National Cancer Institute, the surgeon may remove the cancerous tumor in one of three ways:

- Electrofulguration: electric current is used to kill the cancer cells
- Laser therapy: a narrow beam of powerful light is used to kill the cancer cells
- Cystourethrectomy: the urethra and bladder are removed

Surgical requirements vary depending on the severity of the cancer. The removal of the urethra will require the surgeon to create something called a urinary diversion, meaning another way to urinate will need to be constructed. In some cases, the patient's physician may recommend that men have part or their entire penis removed, which is called a penectomy. If a penectomy (the total removal of the penis) is done, the patient will need plastic surgery to make a new penis. Lymph nodes in the pelvis may also be removed. In women, surgery to remove the urethra, bladder, and/or vagina may be necessary. Plastic surgery will be necessary to create a new vagina.

When a patient's bladder is removed, the surgeon may use part of the small intestine to create a tube so that the patient can urinate and a mouth-like opening, referred to as a stoma, is made surgically on the outside of the body. This procedure is called an ostomy. The patient then uses glue to connect a bag that is designed especially for the purpose of being connected to the stoma. As a patient urinates, the urine collects in the bag. The patient can then throw the bag away and replace it with a new one. The bag is hidden under the patient's clothing. Ostomy patients can be more prone to infection and some patients with sensitive skin may experience occasional skin irritation due to the glue that holds the bag in place.

It is psychologically difficult for some patients to get used to urinating in a bag. Fears of having "accidents" or "smelling bad" sometimes overwhelm ostomy patients. Support groups and special counseling can be very helpful to patients who are having a difficult time adjusting to their new situation.

Based on the severity and extent of the cancer, radiation and/or chemotherapy treatments may be recommended. The prognosis of urethral cancer depends on a variety of factors, such as the tumor's size and location, as well as the extent of the cancer and the patient's general health. For example, in an article published in the *Journal of Urology*, Drs. Grisby and Corn reported that women who have been diagnosed with posterior urethral cancer that do not have tumors larger than 2 centimeters can be effectively treated with radiation alone, surgery alone, or a combination of the two treatment options. In fact, studies such as the one conducted by Dr. Sailer and colleagues, which was also published in the *Journal of Urology*, have shown that 60% of the women diagnosed with posterior urethral cancer that have tumors smaller than 2 centimeters can expect a five-year survival, whereas only 13% of the women can expect a five-year survival if their tumors exceed 4 centimeters.

Coping with cancer treatment

Patients having difficulty coping with the pain associated with cancer and chemotherapy might find it helpful to be referred to a physician who specializes in pain management or a pain clinic. Physicians specializing in the treatment of pain come from a variety of medical backgrounds, such as anesthesiology, urology, and surgery. Because of the complicated nature of cancer and cancer-related pain, ideally a pain management team should be formed that works with the patient's primary care physician, oncologist, and radiologist to provide comprehensive care to the patient.

But what about the emotional pain that is associated with urethral cancer? Much has been written about

QUESTIONS TO ASK YOUR DOCTOR

- How will having a penectomy affect my survival time?
- When is it safe for me to resume sexual relations?
- Are there any clinical trials I should consider joining?
- How successful is the reconstructive surgery?
- How will the treatment affect my ability to have children?
- How will my ability to urinate be affected if I have an ostomy?

coping with the physical side effects of cancer treatment; however, patients with urethral cancer also face emotional challenges associated with their treatment. For example, men and women may be concerned how the treatment will affect their sexual relations. They may have to deal with a variety of psychological issues, such as body image versus self-image. Patients may need to be reminded, especially by family members and friends, that they are more than a collection of body parts. Patients having difficulty dealing with the emotional aspects of their cancer may find it useful to see a psychologist. Psychologists can help patients identify a variety of coping mechanisms designed to enable them to deal with what lies ahead.

It is important for cancer patients to understand that they are not alone. Support groups exist to help patients cope not only with the physical aspects of having cancer, but with the psychological ones as well. Patients should be encouraged to talk about their feelings. The positive support (both emotional and otherwise) provided by caregivers can help to improve a patient's quality of life. In addition, support groups on the Internet have made it possible for patients, even those in rural or remote areas, to reach out to one another in ways that allow anonymity.

Resources

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Lee Ann Paradise

Urostomy

Definition

Urostomy is a surgical procedure that creates an opening (stoma) in the abdominal wall through which urine leaves the body.

Purpose

Doctors perform urostomy when a patient has **bladder cancer**, spinal cord injury, specific types of birth defects, or when the bladder is not functioning properly and must be removed.

Precautions

In an individual who is obese or who has folds in the skin or scars in the abdominal wall, an internal collection sac (reservoir) the patient can empty (catheterize) works better than a passage that lets urine flow out of the body into a collection bag (pouch) worn next to the skin under the clothes.

Description

Urostomy is a form of urinary diversion. Surgeons perform this reconstructive procedure when disease, infection, injury, or congenital abnormality makes it necessary to remove a patient's bladder and create a new channel (conduit) for urine to leave the body.

Surgeons perform urostomy by separating a short piece of the large or small intestine from the rest of the intestine. They attach the separated intestine to the two thick tubes (ureters) that carry urine from the kidneys to the bladder and connect the ureters to the stoma.

Continent and incontinent diversions

An incontinent ostomy drains continuously into a small pouch fitted over the stoma and worn under the

patient's clothes. The patient wears a collection pouch at all times and empties it several times a day.

To perform a continent urinary diversion, the surgeon uses a piece of the patient's intestine to create an internal reservoir to store urine. The patient does not wear an ostomy pouch but empties the reservoir four to six times a day by inserting a drainage tube (catheter) into the stoma.

Types of urostomy

The most common types of urostomy are the ileal conduit, which uses a piece of the small intestine (ileum) and the colonic conduit, which uses a piece of the large intestine (colon). Orthotopic neobladder is a new type of continent diversion that channels urine into the tube that drains urine from the bladder (urethra) and enables the patient to urinate almost normally.

Temporary urostomy does not involve severing the ureters and is most often performed in children.

Doctors consider the likelihood of disease recurring in the pelvis or urethra as well as the patient's gender to determine which type of urostomy is most appropriate. Neobladders are not appropriate for female patients whose cancer involves the bladder neck or male patients with problems affecting the right colon or small bowel.

If bladder cancer has metastasized or cannot be surgically removed, the surgeon may perform a urostomy without removing the patient's bladder.

Preparation

Before undergoing a urostomy, the patient learns where on the abdomen the stoma will be created, what type of collection device (if any) will be worn, and what changes in appearance the operation may cause.

Nurses encourage the patient preparing to undergo an incontinent urostomy to become familiar with the collection device that will be worn after the operation. They may arrange to have someone who has already had the operation (ostomate) reassure the patient preparing for either an incontinent or continent procedure and answer questions about life after the surgery.

Preoperative restrictions

The patient may be told not to eat certain foods before surgery and must fast for eight hours and have a cleansing enema before the operation.

Fluid and **antibiotics** may be given to a patient who is frail.

KEY TERMS

Bladder neck—The narrowest part of the bladder.

Cystoscopy—Diagnostic procedure that allows the doctor to view the entire bladder wall.

Kidney failure—Inability of the kidneys to excrete waste and maintain a proper chemical balance. Also called renal failure.

Aftercare

A patient who has undergone an incontinent diversion wears a collection device that is odor-free, not visible under clothing, disposable or reusable, and available at drug stores or medical supply houses or through the mail.

To prevent urine leakage, infection, skin irritation, and odor, the patient should re-measure the stoma and make any necessary adjustments in the size of the flat sponge-like patch that covers and protects it. This should be done during the first few months after the operation (when shrinkage occurs) or whenever gaining or losing weight. Measuring devices and instructions are included in every box of collection pouches.

Some doctors recommend taking Vitamin C to prevent infection- and odor-causing bacteria from accumulating in the urine. Other recommendations include drinking eight to 10 glasses of water a day to reduce the likelihood of kidney infection.

Risks

Because tumors sometimes develop in neobladders, a patient who undergoes this procedure must have a **cystoscopy** within five years.

Normal results

A patient who has had a urostomy can:

- Shower or bathe with or without the collection pouch.
- Usually wear the clothes worn before the operation.
- Return to work shortly after leaving the hospital, although a doctor's permission is required before doing heavy lifting.
- Enjoy intimate relationships.
- Participate in athletic activities, but should avoid strenuous contact sports like football or wrestling.

Dietary restrictions are rare.

QUESTIONS TO ASK THE DOCTOR

- What type of urostomy will I have?
- Will I have to wear a pouch after the operation?
- Will I be able to take care of myself after the operation?
- Will other people be able to tell that I have had a urostomy?

A woman who has undergone a urostomy should talk with her doctor before becoming pregnant.

Abnormal results

Almost half (40%) of patients who undergo continent diversions and 24.1% of those who undergo ileal or colonic conduits require subsequent surgery to repair leaks or obstructions and correct other surgery-related problems.

A patient who has had a urostomy may also experience:

- kidney damage, infection, or failure
- swelling, shrinkage (stenois), or displacement (prolapse) of the stoma
- infections of the stoma or urinary tract
- fever
- hernia
- diarrhea
- urinary problems
- chills
- pain in the leg or abdomen
- blood or pus in the urine

Resources

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Maureen Haggerty

Uterine cancer *see* **Endometrial cancer**

V

Vaccines

Definition

A cancer vaccine is a method of treating the disease involving administration of one or more substances characteristic of the cancer, called antigens, often in combination with factors that boost immune function. This induces the patient's immune system to attack and eliminate the cancerous cells.

Purpose

Unlike traditional vaccines for infectious diseases, at this time cancer vaccines are not given to prevent the initial development of cancer. Instead, cancer vaccines are a method of treating cancer that has already occurred and are given to patients already diagnosed with cancer.

As a cancer treatment method, the ultimate goal of most cancer vaccines is the elimination of tumor or cancerous cells from the body. Other vaccines are given after the use of more traditional treatments, such as **chemotherapy**, radiation, or surgery, with the aim of suppressing the recurrence of the cancer.

Precautions

No vaccine has yet been approved by the Food and Drug Administration (FDA) for the treatment of cancer. Accordingly, vaccines are not standard treatments and other more traditional treatments should be investigated first. Vaccines are available only through participation in **clinical trials**. Each trial has its own criteria that can limit who can participate. However, many cancers have a current trial for one or more types of vaccines. The American Society for Gene Therapy states that as of late 2000, vaccines were the most common approach to gene therapy being studied by researchers.

Most vaccine trials test the response of the disease with and without the vaccine or the effect of substances added to the vaccine, called adjuvants. Such trials usually only accept patients who have already tried the standard treatment methods. Others test a standard treatment method with and without the addition of the vaccine. A very few compare the standard treatment to the vaccine.

Looking at cancer vaccines overall, this treatment method has been more successful eliminating very small tumors rather than the getting rid of a large tumor load. So if the size of the tumor is significant, a more realistic goal is to shrink the tumor and reduce its effect on the patient's body, rather than total elimination of the cancer.

The complexity of the human immune system has made it very difficult to develop an effective vaccine. Tumors have strategies to evade detection by the immune system. Most notably, they mimic the outward appearance and antigens of the body's own cells. The immune system's built-in lack of response against "self" allows the tumor to escape notice by the body. Now fully aware of this phenomenon, researchers are working to develop methods of circumventing this problem to develop a highly effective vaccine system.

Description

There are three general types of cancer vaccines, those that use whole tumor cells, those that use only one or more substances derived from the tumors, or those that administer primed cells from the patient's immune system.

Whole cell vaccines

Whole cell vaccines are autologous when they contain only inactivated tumor cells from the patient's own tumors. The cells have been isolated from the tumor and made to grow in the laboratory, a process known as creating a cell line. Allogeneic whole cell vaccines are made from inactivated tumor cells isolated from one or more other people. The main advantage to autologous vaccines is the direct relation between the vaccine and

the tumor target. However, because of the screening of self antigens away from a body's own immune system, **immune response** to tumor antigens in autologous whole cells vaccines can be low.

Allogeneic vaccines avoid some of the problems of autologous vaccines. First, cell lines do not have to be created for each patient, a labor-intensive process that can have highly variable results. Second, the same vaccine can be given to all patients, making the response to the vaccine more predictable. Third, a use of a pool of tumor cells can increase the possibility of having the full repertoire of the tumor antigens in the vaccine. This helps to overcome the ability of tumor cells to escape notice by the immune system. Finally, by using well-characterized cell lines, it is much easier for the researcher to add genetic modifications that increase the immune system's response to the cells.

Isolated antigen vaccines

There are many kinds of vaccines that deliver only a portion of the tumor cell that will elicit an immune response, called an antigen. Some antigens are unique to a cancer type, some are unique to an individual tumor, while a very few are found in more than one cancer type. For example, vaccines against telomerase and human chorionic gonadotripin (hCG), two proteins produced by many cancers, have been developed, raising hopes for the development of a universal cancer vaccine.

The most common kind of antigen used in cancer vaccines is a protein or a part of a protein. The protein can actually be isolated from the tumor cells, or more commonly, produced in large quantity using genetic engineering techniques. When a part of a protein is used, experimental efforts generally preceded the vaccine production to determine what parts of the protein were often the target of immune responses. Parts of proteins that elicit immune responses are called epitopes.

Antigens do not necessarily have to be proteins. Immune responses are also mounted against the carbohydrate (sugar) molecules present on the surface of the proteins. Tumor proteins can have unusual carbohydrate structures that set them apart from cells from normal tissue. Carbohydrates are also found in abundant numbers on the surface of the tumor cells. Accordingly, researchers have developed cancer vaccines that combine the tumor-characteristic carbohydrates anchored on protein bases. These vaccines are being tested for their ability to reduce the recurrence of **prostate cancer**.

Vaccines can also contain the naked genetic material encoding the protein (either deoxyribose nucleic acid, DNA, or ribose nucleic acid, RNA). After the genetic material gains entry to the cell, the cellular machinery uses it to produce the antigen and an immune response is mounted against it. Animal studies have found that these types of vaccines are very dependent on the particular antigen and the mode of administration of the vaccine. A unique method of delivery used with DNA or RNA vaccines is the coating of tiny gold beads with the genetic material and shooting the beads into the skin.

Genetically engineered viruses can also be used to bring the DNA or RNA into the cell. When used in this way the viruses are called viral vectors. One example of a viral vector currently being used as a cancer vaccine is one based on the adenovirus. When viruses are used as vectors they have been altered to no longer cause disease, but they do retain the ability to infect human cells. Instead of making new viruses, the infected cells make the desired antigen, and the body will respond against it. Viral vectors can also carry the genetic instructions for factors, called cytokines, which boost the immune system's response to the antigen.

Antigen-presenting cell (APC) vaccines

Vaccines can also be made that contain cells from the patient's own immune system, in particular antigen-presenting cells (APCs). These cells play a central role in the development of an immune response against a particular antigen. Specifically, APCs ingest the antigen and present them to the T cells, a type of immune cells responsible for targeting and killing cells seen as foreign to the body. If T cells are exposed to the antigen by an APC, as opposed to seeing the antigen on the cell itself, they are more strongly activated. That is, more T cells that specifically attack that antigen are produced and the immune response against the foreign cell is stronger.

Dendritic cells are a type of APC that is most effective in activating T cells. For this reason, they are often the kind of cells used in APC vaccines. Unfortunately, the number of dendritic cells circulating in the blood at any one time is relatively low. However, new techniques have been developed that allow that small number of dendritic cells to be isolated and then stimulated outside the body to result in a usable number. During stimulation, the dendritic cells are exposed to the tumor antigen, a process known as priming. Thus, when injected into the body, the dendritic cells are primed to recruit large numbers of T cells specific against the tumor antigen.

Cyokines and adjuvants

Because of the ability of tumor cells to escape detection by the immune system, an important component of many cancer vaccines is the addition of biological factors or chemical adjuvants to help boost immune response. One type of adjuvant is a cytokine, a factor

normally produced by cells of the immune system to help recruit cells to the site of the foreign cells or help T cells function. Some examples of cytokines used in vaccines are granulocyte/macrophage colony stimulating factor (GM-CSF, or sargramostim), the interleukins (especially IL-2), the **interferons** (INFs), and **tumor necrosis factor** alpha (TNF-α).

Adjuvants are chemical additions to vaccines that help boost the response to the contained cells or antigens. Adjuvants are derived from a variety of sources and can be isolated from animals, plants, or are synthetic chemical compounds. Several adjuvants in use with cancer vaccines are keyhole lympocianin (KLH, derived from shell-dwelling sea animals), incomplete Freud's adjuvant (IFA, mineral oil and an emulsifying agent), and QS-21 (a chemical derived from the soapbark tree).

Administration

The particular administration method and schedule will vary from clinical trial to clinical trial. Administration methods can include intradural (injection within the skin), subcutaneous (injection below the skin), injection into the lymph nodes, or intravenous (injection into the veins). Typically, vaccines are administered as a series of several doses (initial challenge and boosters). Many clinical trials utilize various administration methods and timing strategies in order to try to determine the best means of inducing an anti-tumor immune response.

Preparation

Before enrolling in a clinical trial, patients should discuss the potential benefits and risks with their doctor. Clinical trials can be located by contacting the research institutes directly or by searching the Internet. A particularly good site for getting information about clinical trials for cancer treatment is run by the National Cancer Institute (<http://www.clincialtrials.gov>).

Aftercare

One of the most striking advantages of vaccines compared to other cancer treatments is the relatively low incidence of side effects. Particularly if IFN is used as an immunoadjuvant, patients sometimes experience flu-like symptoms. However, other than some soreness at the site of injection, vaccine patients generally have no adverse reactions to this kind of treatment.

Risks

The greatest risk with cancer vaccines is that there will be no immune response and the treatment will be ineffective. Although serious adverse reactions to the antigens, such as the attack of healthy cells, are theoretically possible, these fears have not materialized. Other than some mild adverse reactions, such as **fever** and redness of the skin at the injection site, vaccine treatment appears relatively low-risk in the traditional sense.

KEY TERMS

Adjuvant—A substance added to a vaccine to increase the immune system's response to the vaccine contents.

Allogeneic—A type of vaccine made up of tumor cells derived from persons other than the patient.

Antigen—A substance characteristic of a tumor that evokes an immune response.

Antigen presenting cell—A cell of the immune system that ingests antigens and exposes them to cells of the immune system in a way that activates the cells to seek out and destroy any other cells displaying that antigen.

Autologous—A type of vaccine made up of tumor cells from the patient's own tumor.

Cytokine—A substance made by cells of the immune system that increases the response to a foreign substance.

Dendritic cell—A special type of antigen-presenting cell that is effective in stimulating T cells.

Epitope—A portion of a protein or other molecule that is the specific target of an immune response.

Normal results

Based on a review of published clinical trials as of 2000, normal results for this treatment is, unfortunately, little or no effect. Although a response by the immunized patient's T cells against the tumor is often documented by testing, the effect on disease is generally marginal. These results could be at least partially due to the selection process for patients in the trials, who are often suffering from late-stage cancers.

Abnormal results

For each trial, there are a small percentage of patients who have complete, partial, or mixed response to the vaccine. Others show a stabilization of the disease where deterioration of condition would be expected. As

QUESTIONS TO ASK THE DOCTOR

- Have all the standard treatment methods for my cancer been tried?
- Is there a vaccine in clinical trials for my kind of cancer?
- Do I fulfill the requirements necessary for the clinical trial for this vaccine?
- Has this vaccine been tried on human patients before?
- If so, what were the results?

traditional treatments were often unsuccessful with these patients, these results are significant. However, the very low rate of success underscores the complexity of the human immune system, the number of variables in the vaccine method, and the amount of research that will need to be done to develop an effective vaccine treatment for this disease.

See also Immunologic therapy; Monoclonal antibodies.

Resources

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Vaginal cancer

Definition

Vaginal cancer refers to an abnormal, cancerous growth in the tissues of the birth canal (vagina).

Description

Vaginal cancer is rare and accounts for only 1% to 2% of all **gynecologic cancers**. In the United States, there are approximately 2,000 cases of vaginal cancer diagnosed, and approximately 600 deaths, each year. Vaginal cancer can be either primary or metastatic. Cancer that originates in the vagina is called primary vaginal cancer; if cancer spreads to the vagina from another site, it is called metastatic cancer. Eighty-percent of vaginal cancers are metastatic. Metastatic cancers carry the name of the primary cancer site. For instance, cancer that has spread from the cervix to the vagina would be called "metastatic cervical cancer," not "vaginal cancer."

The vagina is a short tube that extends from the outer female genitalia (vulva) to the opening to the uterus (cervix). It serves to receive the penis during sexual intercourse, as an outlet for shed tissue and blood during menstruation, and as a passageway for a baby during childbirth. Most cancers are located in the upper third of the vagina.

Squamous **carcinoma** is the most common type of vaginal cancer and accounts for 85% of cases. Infrequent types of vaginal cancer include adenocarcinoma, **melanoma**, and **sarcomas**. Adenocarcinoma is usually found in young women (ages 12 to 30 years) while squamous cell cancer (squamous carcinoma) is usually found in older women (ages 60 to 80 years). Although vaginal melanoma can afflict adult women of any age, women are on average in their fifties at the time of diagnosis.

Demographics

Vaginal cancer is most common in women who are between the ages of 60 and 80.

Causes and symptoms

Cancer is caused when the normal mechanisms that control cell growth become disturbed, causing cells to grow and divide without stopping. This is usually the result of damage to the genetic material of the cell (deoxyribonucleic acid, or DNA). The cause of vaginal cancer is not known.

Symptoms of vaginal cancer appear when the cancer has become more advanced. Approximately 20% of vaginal cancer cases are asymptomatic (produce no symp-

toms) and are diagnosed following an abnormal **Pap test**. Symptoms of vaginal cancer include:

- abnormal vaginal bleeding or discharge
- pain during intercourse
- pain in the pelvic area
- difficult or painful urination
- constipation

Diagnosis

The diagnosis of vaginal cancer is made by physical examination and laboratory analysis of tissue samples. During the physical examination, the physician will place one or two fingers into the vagina and press down on the lower abdomen with his or her free hand to feel (palpate) the reproductive organs and any masses. During a routine speculum examination, the physician will obtain a sample of cervical and vaginal cells (using a swab, brush, or wooden applicator) for laboratory analysis (Pap test).

A special magnifying instrument, called a colposcope, may be used to view the vagina. Additionally, the surface of the vagina may be treated with a dilute solution of acetic acid, which causes some abnormal areas to turn white. Squamous carcinoma and adenocarcinoma usually appear as a growth on the surface of the vagina. Squamous carcinoma may present as an open sore (ulcer). Adenocarcinoma may lie deeper so that it is not visible and detected only by palpation. Vaginal melanoma appears as a brown or black skin tag (polypoid), growth attached to the vaginal wall by a stem (pedunculated), nipple-like growth (papillary), or fungus-like growth (fungating). Sarcomas often appear as a grape-like mass.

If any area appears abnormal, a tissue sample (**biopsy**) will be taken. The biopsy can be performed in the doctor's office with the use of local anesthetic. A small piece of tissue, which contains the suspect lesion with some surrounding normal skin and the underlying skin layers and connective tissue, will be removed. Small lesions will be removed in their entirety (excisional biopsy). The diagnosis of cancer depends on a microscopic analysis of this tissue by a pathologist.

Chest x rays and routine blood work are commonly employed in the diagnosis of any cancer. Endoscopic examination of the bladder (**cystoscopy**) and/or rectum (proctoscopy) may be performed if it is suspected that the cancer has spread to these organs.

Treatment team

The treatment team for vaginal cancer may include a gynecologist, gynecologic oncologist, radiation oncologist, plastic surgeon, gynecologic nurse oncologist, sexual therapist, psychiatrist, psychological counselor, and social worker.

Clinical staging, treatments, and prognosis

Clinical staging

The International Federation of Gynecology and Obstetrics (FIGO) has adopted a clinical staging system for vaginal cancer that is used by most gynecologic oncologists. Vaginal cancer is categorized into five stages (0, I, II, III, and IV) that may be further subdivided (A and B) based on the depth or spread of cancerous tissue. The FIGO stages for vaginal cancer are:

- Stage 0. Cancer is confined to the outermost layer (epithelium) of vaginal cells and is called carcinoma *in situ* or vaginal intraepithelial neoplasia (VAIN).
- Stage I. Cancer is confined to the vagina.
- Stage II. Cancer has spread to the tissues near the vagina.
- Stage III. Cancer has spread to the bones of the pelvis, local lymph nodes, and/or other reproductive organs.
- Stage IV. Cancer has spread to the bladder, rectum, or other parts of the body.

Treatments

The treatment of vaginal cancer varies considerably and depends on the type of cancer, stage of cancer, and the patient's age and overall health. Surgery is the most common treatment for vaginal cancer. **Radiation therapy** and **chemotherapy** are often used as adjuvant therapy to complement the surgical treatment.

SURGERY The amount of tissue removed depends upon the stage and type of cancer. The local lymph nodes may also be removed (lymphadenectomy). Laser surgery, which destroys the cancerous cells, may be used in the treatment of stage 0 vaginal cancer. With a wide local excision, the cancerous tissue and some surrounding healthy tissue is cut out. Wide local excisions may require skin grafts to repair the vagina.

For more extensive cancer, the vagina may be removed (vaginectomy). Following vaginectomy, skin grafts and plastic surgery are used to create an artificial vagina. Vaginal cancer that has spread to the other reproductive organs would be treated by radical hysterectomy in which the uterus, fallopian tubes, and ovaries are removed. Cancer that has spread beyond the reproductive organs may be treated by pelvic **exenteration**, in which the vagina, cervix, uterus, fallopian tubes, ovaries, and, as necessary, the lower colon, bladder, or rectum are removed.

Surgical complications include urinary tract infection, wound infection, temporary nerve injury, fluid accumulation (edema) in the legs, urinary **incontinence**, falling or sinking of the genitals (genital prolapse), and blood clots (thrombi).

RADIATION THERAPY Radiation therapy may be used as the sole treatment of vaginal cancer or as an adjuvant therapy to aid surgery. Radiation therapy uses high-energy radiation from x rays and gamma rays to kill the cancer cells. Radiation given from a machine that is outside the body is called external radiation therapy. Radiation given internally is called internal radiation therapy or brachytherapy. Sometimes applicators containing radioactive compounds are placed inside the vagina (intracavitary radiation) or directly into the cancerous lesion (interstitial radiation). External and internal radiation may be used in combination to treat vaginal cancer.

The skin in the treated area may become red and dry and may take as long as a year to return to normal. **Fatigue**, upset stomach, **diarrhea**, and nausea are also common complaints of women having radiation therapy. Radiation therapy in the pelvic area may cause the vagina to become narrow as scar tissue forms. This phenomenon, known as vaginal stenosis, makes intercourse painful.

CHEMOTHERAPY Chemotherapy is not very a very successful treatment of vaginal cancer and is generally reserved for patients with advanced disease. Chemotherapy uses anticancer drugs to kill the cancer cells. The drugs are usually given by mouth (orally) or intravenously. They enter the bloodstream and can travel to all parts of the body to kill cancer cells. Generally, a combination of drugs is given because it is more effective than a single drug in treating cancer. For vaginal cancer, anticancer drugs may be put into the vagina (intravaginal chemotherapy).

The side effects of chemotherapy are significant and include stomach upset, vomiting, appetite loss (anorexia), hair loss (alopecia), mouth or vaginal sores, fatigue, menstrual cycle changes, and premature menopause. There is also an increased chance of infections.

Prognosis

Survival is related to the stage and type of vaginal cancer. The five-year survival rates for squamous carcinoma and adenocarcinoma of the vagina are: 96%, stage 0; 73%, stage I; 58%, stage II; 36%, stage III; and 36%, stage IV. With a five-year survival rate of less than 20%, melanoma has a poor prognosis. Vaginal cancer most commonly spreads (metastasizes) to the lungs, but may spread to the liver, bone, or other sites.

KEY TERMS

Adjuvant therapy—A treatment that is intended to aid the primary treatment. Adjuvant treatments for vaginal cancer are radiation therapy and chemotherapy.

Biopsy—Removal of a small piece of tissue for microscopic examination. This is done under local anesthesia and removed by either using a scalpel or a punch, which removes a small cylindrical portion of tissue.

Colposcope—An instrument used for examination of the vagina and cervix. The instrument includes a light and magnifying lens for better visualization.

Intracavitary radiation—Radiation therapy for vaginal cancer in which a cylindrical container holding a radioactive substance is placed into the vagina for one or two days.

Metastasis—The movement of cancer cells from one area of the body to another. This occurs through the blood vessels or the lymph vessels.

Pelvic exenteration—Surgical removal of the organs of the pelvis which includes the uterus, vagina, and cervix.

Squamous cells—Scale-like cells that cover some body surfaces and cavities.

Vaginectomy—Surgical removal of the vagina. An artificial vagina can be constructed using grafts of skin or intestinal tissue.

Alternative and complementary therapies

Although alternative and complementary therapies are used by many cancer patients, very few controlled studies on the effectiveness of such therapies exist. Mind-body techniques such as prayer, biofeedback, visualization, meditation, and yoga have not shown any effect in reducing cancer but can reduce stress and lessen some of the side effects of cancer treatments.

Clinical studies of hydrazine sulfate found that it had no effect on cancer and even worsened the health and well-being of the study subjects. One clinical study of the drug amygdalin (Laetrile) found that it had no effect on cancer. Laetrile can be toxic and has caused death. Shark cartilage, although highly touted as an effective cancer treatment, is an improbable therapy that has not been the subject of clinical study.

The American Cancer Society has found that the ''metabolic diets'' pose serious risk to the patient. The

effectiveness of the macrobiotic, Gerson, and Kelley diets and the Manner metabolic therapy has not been scientifically proven. The Food and Drug Administration (FDA) was unable to substantiate the anticancer claims made about the popular Cancell treatment.

There is no evidence for the effectiveness of most over-the-counter herbal cancer remedies. However, some herbals have shown an anticancer effect. Some studies have shown that polysaccharide krestin (PSK), a substance from the mushroom *Coriolus versicolor*, has some effectiveness against cancer. In a small study, the green alga *Chlorella pyrenoidosa* has been shown to have anticancer activity. In a few small studies, evening primrose oil has shown some benefit in the treatment of cancer. Herbals can have a negative impact on conventional treatment; patients must discuss herbal use with a physician.

For more comprehensive information, the patient should consult the book on complementary and alternative medicine published by the American Cancer Society listed in the Resources section.

Coping with cancer treatment

The patient should consult her treatment team regarding any side effects or complications of treatment. Vaginal stenosis can be prevented and treated by vaginal dilators, gentle douching, and sexual intercourse. A water-soluble lubricant may be used to make sexual intercourse more comfortable. Women with a reconstructed vagina will need to use a water-soluble lubricant during sexual intercourse. Many of the side effects of chemotherapy can be relieved by medications. Women may wish to consult a psychotherapist and/or join a support group to deal with the emotional consequences of cancer and vaginectomy.

Clinical trials

As of 2001, there are no **clinical trials** underway that were specific for vaginal cancer. Women should consult with their treatment team to determine if they are candidates for any ongoing studies.

Prevention

Risk factors for vaginal cancer include:

- Diethylstilbestrol (DES). Young women whose mothers took DES during pregnancy are at a higher risk of developing vaginal cancer, particularly clear cell carcinoma. Between 1945 and 1970, DES was prescribed to pregnant women who were at risk of miscarriage.
- **Cervical cancer**. Women with a history of cervical cancer have a high risk of developing vaginal cancer.
- Hysterectomy. Up to half of all patients with vaginal cancer have had a hysterectomy. Their vaginal cancer may actually represent an earlier spread from the cervix.
- Chronic irritant vaginitis. Chronic irritation to the vagina, particularly from use of a vaginal pessary, is associated with vaginal cancer. A pessary is an instrument that is placed into the vagina to support the uterus or prevent pregnancy (contraception).
- Vaginal adenosis. This condition, in which cells that resemble those of the uterus are found in the vaginal lining, places a woman at a higher risk of developing vaginal cancer.

QUESTIONS TO ASK THE DOCTOR

- What type of cancer do I have?
- What stage of cancer do I have?
- What is the five-year survival rate for women with this type and stage of cancer?
- Has the cancer spread?
- What are my treatment options?
- How much tissue will you be removing? Can you remove less tissue and complement my treatment with adjuvant therapy?
- What are the risks and side effects of these treatments?
- What medications can I take to relieve treatment side effects?
- Are there any clinical studies underway that would be appropriate for me?
- What effective alternative or complementary treatments are available for this type of cancer?
- How debilitating is the treatment? Will I be able to continue working?
- Are there any restrictions regarding sexual activity?
- How is a vaginal reconstruction performed?
- How will a vaginal reconstruction affect sexual functioning?
- Are there any local support groups for vaginal cancer patients?
- What is the chance that the cancer will recur?
- Is there anything I can do to prevent recurrence?
- How often will I have follow-up examinations?

- Human papilloma virus (HPV) infection. Infection by this sexually transmitted virus, the cause of genital warts, increases a woman's risk of developing squamous carcinoma.
- Smoking. There appears to be an association between tobacco use and vaginal cancer.

All women, even those who have had a hysterectomy or are past menopause, should get an annual pelvic examination and Pap test. Women who had a hysterectomy because of cancer may benefit from more frequent Pap tests. The earlier that precancerous abnormalities or vaginal cancer are detected, the better the prognosis. Women whose mothers took DES during pregnancy and those with vaginal adenosis should be screened regularly. Women can reduce the risk of contracting HPV by avoiding sexual intercourse with individuals who have had many sexual partners, limiting their number of sexual partners, and delaying first sexual activity until an older age. Avoiding tobacco products may reduce a woman's risk of developing vaginal cancer.

Special concerns

Of special concern to women undergoing treatment of vaginal cancer is the effect surgery and/or radiation therapy will have on sexual functioning. Women of childbearing age may worry about their fertility and whether or not they will be able to bear children. **Depression**, due to the affects of surgery on **body image** and **sexuality**, may occur. Complications, both short term and long term, following extensive surgical treatment of vaginal cancer are not uncommon.

See also Cystoscopy; Fertility issues.

Resources

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) ACS-2345. <http://www.cancer.org>.

Cancer Research Institute. 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

Gynecologic Cancer Foundation. 401 North Michigan Ave., Chicago, IL 60611. (800) 444-4441 or (312) 644-6610. <http://www.wcn.org/gcf>.

National Institutes of Health, National Cancer Institute. 9000 Rockville Pike, Bethesda, MD 20982. (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

Belinda Rowland, Ph.D.

Valacyclovir HCl *see* **Antiviral therapy**

Valrubicin

Definition

Valrubicin (also known as Valstar) is a chemotherapeutic drug that interferes with the metabolism of DNA, thus disrupting the proliferation of cells, including cancer cells.

Purpose

Valrubicin is an antineoplastic drug that is used as a treatment for a form of **bladder cancer** called papillary bladder cancer when the bladder cannot be surgically removed due to increased risk of morbidity or mortality. It is also being tested as treatment for several other types of carcinoma *in situ*.

Description

The Food and Drug Administration approved valrubicin for bladder cancer treatment in 1998. As of 2000, it was being tested in **clinical trials** for both bladder and **ovarian cancer** treatments. It is an anthracycline-like compound that acts by penetrating cells and disrupting the dividing cell cycle by interfering with DNA metabolism. Valrubicin acts by inhibiting nucleoside incorporation into nucleic acids, thus, causing major damage to

DNA. Research performed in 1999 indicated that valrubicin entered cells faster than **doxorubicin**, another anthracycline. Research has also shown that complete response is seen in one in five patients.

Recommended dosage

Valrubicin is only available in instillation form and can only be administered under the supervision of a physician. During initial clinical trials patients received doses ranging from 200 milligrams to 900 milligrams each week. The normal dose is 800 milligrams once a week for six weeks. However, dosing may vary from patient to patient. The drug is administered intravesically (directly into the bladder) through a catheter tube that penetrates into the bladder wall. Once delivered to the bladder the solution should be maintained in the bladder for approximately two hours.

During clinical trials for ovarian cancer, valrubicin is administered through the abdomen.

Precautions

There are other bladder problems that may affect the use of valrubicin. Patients with bladder irritation can have an increased risk of unwanted effects. Patients with perforated bladders should not take this medication. Patients with small bladders could have trouble holding all of the medication. Finally, if patients have urinary tract infections, they should use caution when taking this medication.

Valrubicin has not been studied in pregnant women, but it has been studied in pregnant animals. In animals it can cause birth defects. Therefore, women who are pregnant or breast-feeding should not take valrubicin. Additionally, women should not become pregnant while on this medication. Men taking this medication should not engage in procreative activities. Both men and women should use appropriate forms for contraception to avoid causing pregnancy.

There have not been appropriate studies done specifically on children or the elderly to determine the risk of using this medication in these populations. However, this drug is not expected to act differently in the elderly than it does in younger adults.

Side effects

During the six-week course of treatment patients could experience one or more side effects. The most common are loss of bladder control, increased frequency of urination, and blood in the urine. Other less common and rare side effects are bladder pain, pelvic pain, urethral pain, and loss of the sense of taste.

KEY TERMS

Carcinoma *in situ*—A malignant tumor in a preinvasive stage

Instillation—Dropping a liquid into a body part such as the bladder.

Intravesical—Within the bladder.

Urethral—Relating to the urethra, a passageway from the bladder to outside the body

Interactions

As of 2000 there were no known drug-drug interactions with valrubicin.

Sally C. McFarlane-Parrott

See also Daunorubicin; Taste alteration.

Vancomycin *see* **Antibiotics**

Vascular access

Definition

Vascular access is the use of flexible tubes (catheters) that remain inserted into blood vessels for weeks or months, and provide a means of infusing **antibiotics**, **chemotherapy**, pain medications, or **nutritional support** into patients, and enable blood samples to be taken from patients.

Purpose

Cancer patients may require a variety of treatments over extended periods of time. Many of these treatments are infused directly into the bloodstream (intravenous or IV therapy). For example, a cancer patient may need chemotherapy given through a vein, as well as blood tests requiring frequent samples to be taken from their veins. Indwelling catheters, which stay in place for weeks or months, save the patient the discomfort of undergoing frequent needle sticks (venipuncture), and prevent veins from the trauma of repeated punctures and accidental release of harsh chemical agents into skin and subcutaneous tissues. The catheters are used for continuous, as well as intermittent, treatments and procedures.

Description

The two types of indwelling catheters are external and internal. These devices have been in use since the 1970s.

When deciding which catheter to use, the physician looks at the:

- patient's age and size
- length of time the catheter will be in place
- purpose of the catheter
- patient's previous history with indwelling devices
- condition of the blood vessels

Physicians also consider their own preferences, as well as the treatment team suggestions and any special needs the patient may have.

External catheters are usually made of polyurethane for short–term use, and silicone for long–term use. Long–term devices have an internal cuff surrounding them to prevent catheter movement and infection. They have one to three openings, called lumens. One may be used for chemotherapy, a second for nutritional support, and the third for drawing blood samples. The catheters may be inserted into a central vein in the neck or chest, or an arm vein, called a peripheral vein.

External central catheters

External central catheters are divided into the types designed to stay in place for just a week or so, and the long–term devices commonly known as Broviac, Groshong, and Hickman, which can remain in place for months. The short–term devices are placed directly into a vein, while the long–term catheters are tunneled under the skin to the point where they enter a central blood vessel, such as the cephalic, jugular or subclavian vein. Central catheters are inserted using sterile, surgical technique.

External peripheral catheters

A peripherally inserted central catheter, or PICC, is inserted through the arm, and threaded into a central vein. With proper insertion and care, a PICC can remain in place for months. It may be inserted in the patient's room by a specially trained nurse. A PICC may limit arm movement, and is usually placed in the patient's least dominant arm. For example, the left arm would be the ideal PICC insertion site for a right–handed person. However, if a procedure such as breast surgery has been performed on one side, the PICC will most likely be inserted into the arm on the other side.

KEY TERMS

Broviac—Long–term external central venous catheter.

Groshong—Long–term external central venous catheter, similar to Broviac or Hickman types, but with a different tip.

Hickman—Long–term external central venous catheter.

Lumen—An external opening in the catheter used for putting fluids in or drawing blood out.

Mediport—A defunct brand of implantable port now used to refer to any implantable port.

Pasport—Long–term implantable port inserted in the arm.

PICC—Long–term silicone or polyurethane catheter inserted into the arm, and threaded into central circulation.

Portacath—Long–term implantable port.

Internal catheters

An internal catheter, such as a Portacath or Pasport, is commonly called an implantable mediport because the catheter connects to a pocket, or reservoir, located under the skin, either in the chest or arm. While the system is entirely internal, the pocket is located near the surface and can be felt through the skin. The range of catheter materials includes plastic and titanium. Over the years, these devices have gotten smaller in size, making them more comfortable for patients. An implantable port is inserted and removed in a surgical or radiology setting using sterile technique. Functionality can be determined by injecting contrast material into the port, a procedure referred to as a port-o-gram. Fluid flow is regulated by a pump located on the outside or implanted internally during a surgical procedure. External pumps are usually portable so patients can move around.

Preparation

External long–term indwelling catheters, such as Hickmans, and internal catheters, such as Portacaths, are inserted in a surgical setting. Patients are positioned with their legs elevated during the procedure and are usually given a local anesthetic to help them relax. Some pediatric patients are given additional anesthesia.

Aftercare

After a long–term external or internal catheter is in place, patients have a chest **x ray** to assure that it is in the

QUESTIONS TO ASK THE DOCTOR

- What type of catheter will I have?
- Why was this particular type chosen?
- Will insertion be an outpatient procedure or require a hospital stay?
- Who will insert the catheter?
- How should I prepare for insertion?
- What are the risks of a complication during insertion?
- Will any special care be needed immediately after it is put into place?
- What treatments will I receive through the catheter?
- What special care does the device require?
- What are the symptoms of a catheter problem?
- Will the catheter cause any physical limitations?
- How long will my catheter be in place?
- How will the catheter be removed?

proper position, and that the procedure has occurred without complications.

Special concerns

Catheter Care

Indwelling catheters require frequent care so that they work properly and stay clean. The devices must be cleaned daily and handled carefully. They are flushed with **heparin** or saline, usually every day or every other day, depending on the device. Care techniques vary with the different catheters.

Risks

There are certain complications that may occur during catheter placement. Pneumothorax (air in the pleural cavity) or hemothorax (blood in the pleural cavity) rarely occurs during insertion, and is uncommon after the catheter is in place.

The catheter may leak due to a defect or as a result of being pinched between the collarbone and rib. More commonly, a blockage in the tubing may occur. The first sign of this problem is usually difficulty withdrawing blood, and the blockage can be confirmed with a chest x ray. Flushing will sometimes clear the blockage.

Another problem is that a catheter can move over the course of time. To get a dislodged catheter back into place, patients are sometimes instructed to raise their arms or attempt other maneuvers. If catheter movement recurs, the device will repeatedly malfunction, and may need to be removed.

Another risk over time is that of a vein thrombosis, commonly called a blood clot. The treatment varies for each patient. It may be as simple as changing the arm position or, in more serious cases, may involve removing the catheter. This condition may or may not have symptoms, but is important to diagnose because blood clots that break loose (emboli) can travel around the bloodstream and become potentially fatal.

Infection presents another risk, and may occur on the surface or internally, along the tubing itself. An infection at the surface is usually red, tender to the touch, and may contain discharge. A gram–positive bacteria, such as staphylococcus, is the most common culprit, although other bacteria have been found in these infections. Treatment is determined by the seriousness of the infection, the site of the problem, and the type of catheter involved. A minor infection may clear up with a topical antibiotic applied to the skin. In more severe cases, such as infections along the tubing, in the bloodstream, or in an implantable port, a course of antibiotics will be prescribed.

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Rhonda Cloos, R.N.

Venoocclusive disease

see **Bone marrow transplantation**

Vinblastine

Definition

Vinblastine is a drug used to treat certain types of cancer. Vinblastine is available under the trade names Velban and Velsar, and may also be referred to as vinblastine sulfate. The drug was previously known as vincaleukoblastine or VLB.

Purpose

Vinblastine is an antineoplastic agent used to treat **Hodgkin's disease**, **non-Hodgkin's lymphomas**, **mycosis fungoides**, cancer of the testis, **Kaposi's sarcoma**, Letterer-Siwe disease, as well as other cancers.

Description

Vinblastine was approved by the Food and Drug Administration (FDA) in 1961.

Vinblastine is a naturally occurring compound that is extracted from periwinkle plants. It belongs to a group of chemicals called alkaloids. The chemical structure and biological action of vinblastine is similar to **vincristine** and **vinorelbine**.

Vinblastine prevents the formation of microtubules in cells. One of the roles of microtubules is to aid in the replication of cells. By disrupting this function, vinblastine inhibits cell replication, including the replication the cancer cells.

Vinblastine is one the most effective treatments for Hodgkin's disease, and is typically used in combination with **doxorubicin**, **bleomycin** and **dacarbazine**. It is also used to treat non-Hodgkin's lymphomas, mycosis fungoides, and Letterer-Siwe disease. Vinblastine is also used to treat cancer of the testis in combination with other cancer drugs, and Kaposi's sarcoma alone, or in combination with other drugs. Vinblastine is also used less frequently to treat other types of cancer.

Recommended dosage

Vinblastine is administered by intravenous injection at intervals of at least seven days. Blood tests may be necessary every seven days to ensure that enough white blood cells are present to continue treatment. The initial dose of vinblastine may be adjusted upward or downward depending on patient tolerance to the toxic side effects of treatment. The minimum recommended treatment duration is four to six weeks.

Precautions

Vinblastine must only be administered by individuals experienced in the use of this cancer chemotherapeutic agent. Vinblastine must only be administered intravenously, that is, directly into a vein. Accidental administration of vinblastine into the spinal cord fluid is a medical emergency that may result in death. Vinblastine has a low therapeutic index. It is unlikely there will be therapeutic benefit without toxic side effects. Certain complications can only be managed by a physician experienced in the use of cancer chemotherapeutic agents.

Because vinblastine is administered intravenously, the site of infusion and surrounding tissue should be monitored for signs of inflammation and irritation.

Adverse side effects are more likely in patients with malnutrition or skin ulceration.

Blood tests may be necessary to ensure that the number of white blood cells is adequate for treatment to continue. Vinblastine is not recommended for use in patients with low white blood cell levels. Infections should also be controlled before vinblastine treatment.

Patients should inform their physician if they experience sore throat, **fever**, chills, or sore mouth and any serious medical event.

Vinblastine may cause harm to a fetus when administered to pregnant women. Only in life-threatening situations, should this treatment be used during pregnancy. Women of childbearing age are advised not to become pregnant during treatment. Women should stop nursing before beginning treatment, due to the potential for serious adverse side effects in the nursing infants.

Side effects

The side effects of vinblastine treatment are usually related to the dose of drug and are generally reversible. Toxic side effects are more common in patients with poor liver function. Studies have also shown that patients with advanced prostate cancer experienced toxic side effects of estramustine phosphage (EMP) plus vinblastine (VBL) and from EMP alone.

A decrease in the number of white blood cells is the principal adverse side effect associated with vinblastine treatment. Blood tests will allow a doctor to determine if there are an adequate number of white blood cells to begin or continue treatment. **Nausea and vomiting** may occur, for which antiemetic agents are usually effective. Shortness of breath is a potentially severe side effect that patients should report to their doctor.

Additional side effects, including loss of appetite (anorexia), **diarrhea**, constipation, pain, rectal bleeding, dizziness, hearing impairment, and hair loss (alopecia) may occur.

KEY TERMS

Alkaloid—A nitrogen-containing compound occurring in plants.

Microtubles—A tubular structure located in cells that help them to replicate.

Therapeutic index—A ratio of the maximum tolerated dose of a drug divided by the dose used in treatment.

Interactions

Drugs that may alter the metabolism of vinblastine, particularly itraconazole, should be used with caution due to the potential for interactions. Hearing impairment may be enhanced when vinblastine is used with other drugs that affect the ear. These drugs include platinum-containing **antineoplastic agents**, such as **cisplatin**. Seizures have been reported in patients taking vinblastine and **phenytoin**. The doses of vinblastine and phenytoin may need to be adjusted to decrease the chance of this problem.

Marc Scanio

Vincristine

Definition

Vincristine is a drug used to treat certain types of cancer. Vincristine is available under the trade names Oncovin, Vincasar, and Vincrex, and may also be referred to as vincristine sulfate, or VCR. The drug was previously known as leurocristine, or LCR.

Purpose

Vincristine is an antineoplastic agent used to treat leukemia, **Hodgkin's disease**, malignant lymphomas, **neuroblastoma**, **rhabdomyosarcoma**, **Wilms' tumor**, as well as other cancers.

Description

Vincristine was approved by the Food and Drug Administration (FDA) in 1984.

Vincristine is a naturally occurring compound that is extracted from periwinkle plants. It belongs to a group of chemicals called alkaloids. The chemical structure and biological action of vincristine is similar to **vinblastine** and **vinorelbine**.

Vincristine prevents the formation of microtubules in cells. One of the roles of microtubules is to aid in the replication of cells. By disrupting this function, vincristine inhibits cell replication, including the replication of the cancer cells.

Vincristine is used in combination with other drugs to treat leukemia. It is also used in combination with other drugs, such as **mechlorethamine**, **procarbazine** and prednisone, to treat Hodgkin's disease. It is also used in combination to treat **non-Hodgkin's lymphomas**, neuroblastoma, rhabdomyosarcoma, and Wilms' tumor. Vincristine is also used less frequently to treat other types of cancer.

Recommended dosage

Vincristine is administered by intravenous injection once per week. The initial dose of vincristine may be adjusted upward or downward depending on patient tolerance to the toxic side effects of treatment.

Precautions

Vincristine must only be administered by individuals experienced in the use of this cancer chemotherapeutic agent. Vincristine must only be administered intravenously, that is, directly into a vein. Accidental administration of vincristine into the spinal cord fluid is a medical emergency that may result in death. Vincristine has a low therapeutic index. It is unlikely there will be therapeutic benefit without toxic side effects. Certain complications can only be managed by a physician experienced in the use of cancer chemotherapeutic agents.

Because vincristine is administered intravenously and is extremely irritating, the site of infusion and surrounding tissue should be monitored for signs of inflammation.

Some experts recommend blood tests to ensure that the number of white blood cells is adequate for treatment to continue. Infections should also be controlled before vincristine treatment starts.

Vincristine is not recommended for use in patients with the demyelinating form of Charcot-Marie-Tooth syndrome.

Vincristine is not recommended for patients receiving **radiation therapy** though a port in the liver.

Vincristine may cause harm to a fetus when administered to pregnant women. Only in life-threatening

KEY TERMS

Alkaloid—A nitrogen-containing compound occurring in plants.

Microtubles—A tubular structure located in cells that help them to replicate.

Therapeutic index—A ratio of the maximum tolerated dose of a drug divided by the dose used in treatment.

situations, should this treatment be used during pregnancy. Women of childbearing age are advised not to become pregnant during treatment. Women should stop nursing before beginning treatment, due to the potential for serious adverse side effects in the nursing infants.

Side effects

The side effects of vincristine treatment are usually related to the dose of drug and are generally reversible. Toxic side effects may be more common in patients with poor liver function.

Toxicity of the nervous system is the principal adverse side effect associated with vincristine treatment. This toxicity may cause numbness, pain, especially of the jaw, tingling, and headaches. Lengthy treatment at high doses may cause even more severe toxicity. Constipation is a common side effect. **Laxatives** and enemas are typically used to prevent severe constipation. Shortness of breath is a potentially severe side effect that patients should report to their doctor. Additional side effects, including rash, an increase or decrease in blood pressure, dizziness, nausea and vomiting, hearing impairment, and hair loss (alopecia) may occur.

Interactions

Drugs that may alter the metabolism of vincristine, particularly itraconazole, should be used with caution due to the potential for interactions. Hearing impairment may be enhanced when vincristine is used with other drugs that affect the ear. These drugs include platinum-containing **antineoplastic agents**, such as **cisplatin**. Seizures have been reported in patients taking vincristine and **phenytoin**. The doses of vincristine and phenytoin may need to be adjusted to decrease the chance of this problem.

Marc Scanio

Vindesine

Definition

Vindesine (desacetyl **vinblastine** amide sulfate) is a synthetic derivative of vinblastine. Vindesine is a **chemotherapy** drug that is given as a treatment for some types of cancer. This drug belongs to the group of anticancer drugs known as vinca alkaloids. Vindesine is also called vindesine sulfate, desacetylvinblastine amide, DAVA, DVA, or VDS, and its brand name, Eldisine.

Purpose

Vindesine is used primarily to treat **acute lymphocytic leukemia**. Less frequently, it is prescribed for use in **breast cancer**, blast crisis of chronic myelocytic leukemia, colorectal cancer, non-small cell lung cancer, and renal cell cancer (kidney cancer).

Description

Vindesine binds to particular proteins and causes cell arrest or cell death. Metabolized by the liver, vindesine is primarily excreted through the biliary system.

Vindesine is used in other countries around the world such as Britain, South Africa, and several European countries, but it is not approved by the Food and Drug Administration, and is thus not commercially available in the U.S. Eli Lilly discontinued Eldisine in Canada in 1998 to make way for newer, more effective vinca alkaloid drugs.

For acute lymphocytic leukemia (ALL), vindesine is effective in both adult and pediatric populations. As an agent used alone, vindesine has produced response rates ranging from 5% to 63% in several clinical studies. Vindesine has been used in combination therapy using the following drugs: **daunorubicin**, **asparaginase**, prednisone, **cytarabine**, and **etoposide**.

The clinical response rate in children (41%) is better than in adults (26%) for treatment of ALL. Vindesine with combination therapy has shown very high response rates in childhood ALL.

For treatment during the blast crisis of chronic myelocytic (or myelogenous) leukemia, overall response rates of 51% have been reported in adults when vindesine was used alone or in combination therapy with prednisone. Efficacy has not been demonstrated in pediatric groups.

Vindesine may be effective in treating breast cancer. When used alone, one clinical trial reported that vinde-

sine showed an overall response rate of approximately 19% in treating advanced breast cancer.

Vindesine in combination with **cisplatin** is one of the most active treatments for non-small lung cancer, but **vinorelbine** substituted for vindesine has shown higher response rates in treating non-small lung cancer.

Vindesine is not effective for treating acute nonlymphocytic leukemia.

Recommended dosage

There are many dosing schedules that depend on the type of cancer, response to treatment, and other drugs that may be co-prescribed. Dosing guidelines also consider the white blood cell count.

Method of administration: Vindesine is injected intravenously through a fine needle (cannula). Alternatively, it may be given through a central line that is inserted under the skin into a vein near the collarbone.

- Intravenous administration for adults: Each one to two weeks a dose of 2-4 mg/m^2 is given; or each three to four weeks 1.5 mg/m^2/day for five to seven days as a continuous infusion is administered.
- Intravenous administration for children: Once a week with 4 mg/m ^{2} or twice weekly with 2 mg/m^2.

Precautions

Vindesine may cause fertility problems in men and women. In addition, it may harm the fetus or may damage sperm; therefore, it is not recommended for women to use vindesine during pregnancy or for men to father a child while taking this drug. The physician should be alerted immediately if pregnancy occurs. Due to possible secretion into breast milk, breast-feeding is not recommended.

Other considerations:

- Vindesine is potentially mutagenic or carcinogenic (cancer-causing).
- Vindesine may cause death if injected intrathecally (into the spinal cord). It is for intravenous use only.
- Prior injection sites should be carefully inspected because tissue damage may occur days or weeks after administration.
- Hepatic dysfunction increases the neurotoxic potential of this drug.
- Alert doctors or dentists about vindesine therapy before receiving any treatment.

KEY TERMS

Acute lymphocytic leukemia—A rapidly progressing disease where too many immature infection-fighting white blood cells called lymphoblasts are found in the blood and bone marrow. It is also known as ALL or acute lymphoblastic leukemia.

Intravenous (or intravenously)—Into a vein.

Vinblastine—A vinca alkaloid. See definition for vinca alkaloid.

Vinca alkaloid—A group of cytotoxic alkaloids extracted from a flower called Madagascar periwinkle. Cytotoxic chemotherapy kills cells, especially cancer cells. Vinca alkaloids are cell cycle phase specific, and exert their effect during the M phase of cell mitosis and cause metaphase cell arrest and death. These drugs are for antineoplastic therapy (chemotherapy) for cancer treatment. Other vinca alkaloids are: vinblastine, vincristine, vindesine, and vinorelbine.

Side effects

Possible side effects of vindesine therapy:

- pain or tenderness at injection site
- Hair loss (alopecia) is common.
- Vindesine can damage the surrounding tissue if it leaks into the tissue around the vein. If vindesine leaks under the skin, a burning or stinging sensation may be felt. Alert the doctor immediately if burning or stinging occurs while the drug is administered or if fluid is leaking from the site where the needle was inserted. Also tell the doctor if the area around the injection site becomes red or swollen at any time.
- Constipation or abdominal cramps. These can be alleviated by drinking plenty of water, eating a high-fiber diet, and light exercise.
- temporary decrease in white blood cell count and platelets
- Numbing of the fingers or toes may occur over the course of treatment. It may take several months to return to normal.
- Diarrhea occurs infrequently.
- mouth sores and ulcers
- Nausea and vomiting rarely occurs.
- Anaphylaxis is rare.
- Jaw pain may be severe, but it is rare.

- Thrombocytopenia (a decrease in the number of platelets in the blood) or thrombocytosis. These conditions are also rare.

Interactions

Vindesine may interact with mitomycin-C (brand name Mutamycin), causing acute bronchospasm within minutes or hours following administration. **Phenytoin** (brand name Dilantin) may also interact with vindesine, leading to decreased serum levels of phenytoin.

Other drug interactions may occur with:

- Itraconazole
- Live virus and bacterial **vaccines**. When taking immune suppressing chemotherapy drugs, live vaccinations should not be given.
- Quinupristin/dalfopristin
- Rotavirus vaccine
- Warfarin

Crystal Heather Kaczkowski, MSc.

Vinorelbine

Definition

Vinorelbine is a drug used to treat certain types of lung cancer. Vinorelbine is available under the trade name Navelbine. The drug may also be referred to as vinorelbine tartrate, or didehydrodeoxynorvincaleukoblastine.

Purpose

Vinorelbine is an antineoplastic agent used to treat non-small cell lung **carcinoma**.

More recently, vinorelbine has been used in the palliative treatment of patients with advanced esophageal cancer and advanced breast cancer. Early reports of its effectiveness are encouraging.

Description

Vinorelbine was approved by the Food and Drug Administration (FDA) in 1994.

Vinorelbine is a semisynthetic derivative of **vinblastine**, a naturally occurring compound that is extracted from periwinkle plants. It belongs to a group of chemicals called vinca alkaloids. The chemical structure and biological action of vinorelbine is similar to vinblastine and **vincristine**.

Vinorelbine prevents the formation of microtubules in cells. One of the roles of microtubules is to aid in the replication of cells. By disrupting this function vinorelbine inhibits cell replication, including the replication the cancer cells.

Vinorelbine is used alone and in combination with **cisplatin** (another anticancer drug) to treat non-small cell lung carcinoma. It has been used in combination with other drugs to treat **breast cancer**. As of 2000 vinorelbine was under investigation for the treatment for **cervical cancer**.

Recommended dosage

Vinorelbine is administered by intravenous injection (directly into a vein) once per week. The initial dose may be adjusted downward depending on patient tolerance to the toxic side effects of treatment. If toxic effects are severe, vinorelbine treatment may be delayed or discontinued.

Precautions

Vinorelbine must be administered only by individuals experienced in the use of this cancer chemotherapeutic agent. Vinorelbine must only be administered intravenously. Accidental administration of vinorelbine into the spinal cord fluid is a medical emergency that may result in death. Vinorelbine has a low therapeutic index, which means it is unlikely there will be therapeutic benefit without toxic side effects. Certain complications can only be managed by a physician experienced in the use of cancer chemotherapeutic agents.

Because vinorelbine is administered intravenously and is extremely irritating, the site of infusion and surrounding tissue should be monitored for signs of inflammation.

Blood tests are recommended to ensure that bone marrow function and the number of white blood cells is adequate for treatment to continue. Infections should also be controlled before vinorelbine treatment starts. Special caution should be used with patients whose bone marrow reserves have been reduced by previous radiation or **chemotherapy** treatment.

Vinorelbine may cause harm to a fetus when administered to pregnant women. Only in life-threatening situations should this treatment be used during pregnancy. Women of childbearing age are advised not to become pregnant during treatment. Women should stop nursing before beginning treatment due to the potential for serious adverse side effects in the nursing infants.

KEY TERMS

Alkaloid—A nitrogen-containing compound occurring in plants.

Microtubles—A tubular structure located in cells that help them to replicate.

Palliative—Referring to a treatment intended to relieve symptoms rather than cure a disease.

Therapeutic index—A ratio of the maximum tolerated dose of a drug divided by the dose used in treatment.

The safety of vinorelbine in children under 18 years of age has not been established.

Side effects

The side effects of vinorelbine treatment are usually related to the dose of drug and are generally reversible. It is possible that toxic side effects may be more common in patients with poor liver function, and should be used with caution in those patients.

Decreased bone marrow function is the principal adverse side effect. This can reduce the number of white blood cells and increase the chance of infections. Patients should report **fever** or chills to their doctors immediately. Patients should also inform their doctor if they experience abdominal pain, constipation, or an increase in shortness of breath.

Toxicity of the nervous system is another side effect. Shortness of breath is a potentially severe side effect that patients should report to their doctor. Additional side effects, including fever, **anemia**, an increase or decrease in blood pressure, dizziness, nausea and vomiting, hearing impairment, and hair loss (alopecia) may occur.

Several cases of heart attacks related to vinorelbine have been reported. A group of French researchers estimates that about 1% of patients treated with vinorelbine will develop heart problems; however, vinorelbine does not appear to have a higher rate of these side effects than other drugs in its class.

Interactions

The use of vinorelbine in combination with another anticancer drug, mitomycin-C, has caused severe shortness of breath. Patients taking vinorelbine and cisplatin are more likely to experience a decrease in the number of white blood cells. This side effect should be carefully monitored to ensure that the number of white blood cells is adequate for treatment to continue. Patients taking vinorelbine and another anticancer drug, **paclitaxel**, may be more likely to experience toxicity of the nervous system, and should be carefully monitored for this. Drugs that may alter the metabolism of vinorelbine should be used with caution due to the potential for interactions.

Patients who are treated with vinorelbine during or following radiotherapy may become hypersensitive to radiation treatment.

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ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657-3000. <www.ashp.org>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

Rebecca J. Frey, PhD

Viruses *see* **Epstein-Barr virus; Human papilloma virus; AIDS-related cancers.**

Vitamins

Definition

Vitamins are compounds that are essential in small amounts for proper body function and growth. Vitamins are either fat soluble: A, D, E, and K; or water soluble: vitamin B and C. The B vitamins include vitamins B_1(thiamine), B_2 (riboflavin), and B_6 (pyridoxine), pantothenic acid, niacin, biotin, **folic acid** (folate), and vitamin B_{12} (cobalamin). Vitamins also may be referred to as micronutrients.

Description

A guide to the amount an average person needs each day to remain healthy has been determined for each vitamin. In the United States, this guide is called the recommended daily allowance (RDA). Consuming too little of certain vitamins may lead to a nutrient deficiency. Consuming too much of certain vitamins may lead to nutrient toxicity.

Consumption of a wide variety of foods that have adequate vitamins and minerals is the basis of a healthy diet. Good nutrition may assist in the prevention of cancer or may help cancer patients to feel better and fight infection during treatments. Obtaining nutrients through food remains the best method for obtaining vitamins, however, requirements may be higher because of the tumor or cancer therapy. Therefore, supplements may be necessary.

The following vitamins are important in a healthy diet and also may assist in **cancer prevention**. Their role in maintaining health and the best food sources are listed below.

Vitamin A (retinal, carotene)

- role in growth and repair of body tissues
- important in night vision
- immune function
- Best sources: eggs, dark green and yellow fruits and vegetables, low-fat dairy products, liver

Vitamin B6 (pyridoxine)

- role in formation of antibodies
- important in carbohydrate and protein metabolism
- red blood cells
- nerve function
- Best sources: lean meat, fish, poultry, whole grains, and potatoes

Folic acid (folate)

- assists in red blood cell formation
- important in protein metabolism
- growth and cell division
- Best sources: green leafy vegetables, poultry, dried beans, fortified cereals, nuts, and oranges

Vitamin C (ascorbic acid)

- resistance to infection
- important in collagen maintenance
- contributes to wound healing
- strengthens blood vessels
- assists in maintaining healthy gums
- Best sources: citrus fruits, tomatoes, melons, broccoli, green and red peppers, and berries

Vitamin E (tocopherol)

- may assist in immune function
- important in preventing oxidation of red blood cells and cell membranes
- Best sources: vegetable oils, wheat germ, nuts, dark green vegetables, beans, and whole grains

Purpose

Specific nutrients have been linked to prevention of several cancers of the colon, breast, prostate, stomach, and other types of tumors. A high intake of fruits and vegetables as well as fiber appears particularly protective, while a diet high in fat has been implicated as a cancer risk.

Vitamins important for cancer prevention

Antioxidant vitamins are believed to protect the body from harmful free radicals that can contribute to diseases such as cancer. Antioxidant vitamins include vitamin A, C, and E. However, doses too high may increase oxidative stress and therefore may increase cancer risk.

A diet rich in fruits and vegetables (containing B6, folate, and niacin) appears to protect against **stomach cancer** and in particular, intestinal cancer.

One study reported that cruciferous vegetables, especially broccoli, brussel sprouts, cauliflower, and cabbage were associated with a decreased risk of **prostate cancer**. Other foods, such as carrots, beans, and cooked tomatoes, also were associated with a lower risk.

A component of Vitamin E, tocotrienol, has been linked to a decreased risk of **breast cancer** in lab animals. Tocotrienol has been shown to readily kill tumor

cells grown in culture. Tocotrienol is not the same type of substance found in generic Vitamin E supplements, but is plentiful in palm oil. Palm oil is difficult to obtain in the Western world, but lower concentrations of tocotrienol are found in rice bran oil and wheat bran oil. In 2004, research showed that the nutrient calcium and vitamin D worked together, not separately, to lower risk of colorectal cancer.

Researchers state that no single nutrient is the answer, but that the effects are cumulative and depend on eating a variety of fruits and vegetables. Because there are many more nutrients available in foods such as fruits and vegetables than in vitamin supplements, food is the best source for acquiring needed vitamins and minerals.

Special concerns

For many years, debate has continued regarding taking vitamin supplements to prevent cancer. In 2004, the U.S. Preventive Services Task Force concluded that the evidence is inadequate to recommend supplementation of vitamins A, C, or E, multivitamins with folic acid, or antioxidant combinations to decrease the risk of cancer. Beta-carotene supplements should not be used in patients with no symptoms because there is no evidence of risk reduction and some evidence that these supplements may cause harm to some patients.

There are concerns regarding antioxidant levels during **chemotherapy** and **radiation therapy**. Researchers report large amounts of Vitamin C are consumed by cancerous tumors during chemotherapy in studies with mice. Vitamin C is an antioxidant that consumes free radicals and is thought to perhaps interfere with the process of killing cancer cells during chemotherapy or radiation therapy. Cancer patients undergoing chemotherapy are advised against taking large amounts of Vitamin C. Another research study also has warned cancer patients about vitamin A and vitamin E during chemotherapy because it has demonstrated a protective effect on cancer cells in mice. These **antioxidants** may protect not only the normal cells from being destroyed, but also may protect dangerous cancer cells from being destroyed during cancer treatment. The researchers suggest an antioxidant-depleted diet may be prudent during cancer therapy.

Smokers are advised not to consume a diet high in beta-carotene (Vitamin A) because research has shown a link to increased lung cancer incidence.

Alternative and complementary therapies

There are a great many claims about particular vitamin and or antioxidants having beneficial health effects. Proper nutrition with an adequate diet is the best way to obtain vitamins, but a supplement may be required when intake is inadequate. It is important to check with a dietitian or doctor before taking nutritional supplements or alternative therapies because they may interfere with cancer medications or treatments.

KEY TERMS

Antioxidant—A substance that prevents damage caused by free radicals.

Cancer—A term for diseases in which abnormal cells divide without control. Cancer cells can invade nearby tissues and can spread through the bloodstream and lymphatic system to other parts of the body.

Free radicals—Free radicals are highly reactive chemicals that often contain oxygen. They are produced when molecules are split to give products that have unpaired electrons. This process is referred to as oxidation.

Malignant (also malignancy)—Meaning cancerous; a tumor or growth that often destroys surrounding tissue and spreads to other parts of the body.

Oxidative stress—A condition in which antioxidant levels are lower than normal. Antioxidant levels usually are measured in blood plasma.

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National Center for Complementary and Alternative Medicine (NCCAM). 31 Center Dr., Room #5B-58, Bethesda, MD 20892-2182. (800) NIH-NCAM, Fax (301) 495-4957. <http://nccam.nih.gov>.

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von Hippel–Lindau disease

Definition

Von Hippel–Lindau disease (VHL) is a rare familial cancer syndrome. A person with VHL can develop both benign and malignant tumors and cysts in many different organs in the body. Tumors and cysts most commonly develop in the brain and spine, eyes, kidneys, adrenal glands, pancreas, and inner ear.

Description

VHL does not have a predictable set of symptoms. VHL affects approximately 1 in 35,000 people, and affects men and women equally. Some families may have different symptoms than other families. Even within a family, there may be people with very mild signs of VHL, and others with more severe medical problems. In one study of a Chinese family with 47 members, four were diagnosed as carriers of the VHL gene while 18 others were diagnosed as having VHL itself. Of these 18 patients, 10 had renal cell carcinoma, 9 had central nervous system hemangioblastomas, and 7 had multiple pancreatic cysts. The age when symptoms develop can range from infancy to late adulthood, although most people with VHL will have some clinical symptoms by age 65. It is important for a person with VHL to have regular physical examinations to check for signs of VHL in all areas of the body that may be affected.

Tumors in the brain and spine, or central nervous system, are called hemangioblastomas. Hemangioblastomas are benign growths (not cancerous), but they may cause such symptoms as headaches and balance problems if they are growing in tight spaces and pressing on surrounding tissues or nerves. The eye tumors in VHL are called retinal angiomas or retinal hemangioblastomas, and may cause vision problems and blindness if they are not treated. Kidney cysts rarely cause problems, but the kidney tumors can be malignant, and are called renal cell **carcinoma**. Tumors in the adrenal glands are called pheochromocytomas. Pheochromocytomas are usually not malignant, but they can cause serious medical problems if untreated. This is because pheochromocytomas secrete hormones that can raise blood pressure to dangerous levels, causing heart attacks or strokes. Benign cysts can be found in the pancreas, and pancreatic islet cell tumors can also occur. These tumors grow very slowly and are rarely malignant. Tumors that grow in the ear are called endolymphatic sac tumors, which can result in hearing loss if untreated. Occasionally men and women with VHL will have infertility problems if cysts are present in certain places in the reproductive organs, such as the epididymis (a duct in the testes)in men or the fallopian tubes in women. A few male patients with VHL develop large testicular masses that can be treated successfully with steroid therapy.

Diagnosis

A clinical diagnosis of VHL can be made in a person with a family history of VHL if he or she has a single retinal angioma, central nervous system hemangioblastoma, or **pheochromocytoma**, or if he or she has renal cell carcinoma. If there is no known family history of VHL, two or more retinal or central nervous system hemangioblastomas must be present, or one retinal or central nervous system hemangioblastoma and one other feature of VHL. Melmon and Rosen published these criteria in 1964, when they first described VHL as a disease with a specific set of features. Because not all people with VHL will meet these diagnostic criteria, VHL may be an under–diagnosed disease. **Genetic testing** can confirm a diagnosis of VHL in a person with clinical symptoms, who may or may not meet the above diagnostic criteria.

Causes

VHL is a genetic disease caused by a mutation of the VHL tumor suppressor gene on chromosome three. It is inherited as an autosomal dominant condition, which means that a person with VHL has a 50% chance of passing it on to each of his or her children. Usually a person with VHL will have a family history of VHL (a parent or sibling who also has VHL), but occasionally he or she is the first person in the family to have VHL. Screening and/or genetic testing of family members can help establish who is at risk for developing VHL. Identification of a person with VHL in a family may result in other family members with more mild symptoms being diagnosed, and subsequently receiving appropriate screening and medical care.

Risks

The United States National Institutes of Health (NIH) has determined risk ranges for a person with VHL to develop certain tumors. Persons with VHL have a 21–72% chance of developing hemangioblastomas of the

brain or spinal cord, a 43–60% chance of developing retinal angiomas, a 24–45% chance of developing cysts and tumors of the kidney, an 8–37% chance of developing pancreatic cysts, and an 8–17% chance of developing pancreatic islet cell tumors. It has been proposed that VHL be divided into subtypes depending on the types of tumors present in a family. It is likely that in the future, specific risk figures will be available for the different types of tumors depending on the specific genetic mutation in a family.

Genetic testing

Almost 100% of people with VHL will have an identifiable mutation in the VHL gene. There have been many different mutations found in the VHL gene, but all persons with VHL in the same family will have the same mutation. If a mutation is known in a family, genetic testing can be done on family members who have not had any symptoms of VHL. A person who tests positive for the family mutation is at risk for developing symptoms of VHL and can pass the mutation on to his or her children. A person who tests negative for the family mutation is not at risk for developing symptoms of VHL, and his or her children are not at risk for developing VHL. Screening is needed for people who test positive for a VHL mutation, and people who are found not to have the family mutation can be spared from lifelong screening procedures. Genetic testing can also be used to determine if a pregnant woman is carrying a fetus affected with VHL. Other techniques may become available which allow selection of an unaffected fetus prior to conception. Families work with a physician, geneticist, or genetic counselor familiar with the most up–to–date information on VHL when having genetic testing, in order to understand the risks, benefits, and current technological limitations prior to testing.

Screening and Treatment

Regular screening and monitoring of tumors in people with VHL allows early detection and treatment, before serious complications can occur. A physician familiar with all aspects of VHL can coordinate screening with a variety of specialists, such as an ophthalmologist for eye examinations. Ultrasounds, **computed tomography** scans (CT), and **magnetic resonance imaging** (MRI) may be used to screen and detect tumors and cysts. Whether or not treatment is necessary depends on the size of the tumor, where it is growing, what the symptoms are, and if the tumor is benign or malignant. Treatment for benign tumors may include surgery or laser treatments. Cancer in people with VHL is treated just as it would be in someone in the general population with that type of cancer. People with VHL who develop cancer have a better prognosis if the cancer is detected at an earlier stage before it has spread. Urine tests, ultrasound, CT and/or MRI screen for pheochromocytomas. It is especially important to screen for pheochromocytomas prior to surgery, because an undiagnosed pheochromocytoma can cause complications during surgery. Prior to becoming pregnant, a woman should have a full physical examination looking for all signs of VHL, but most importantly pheochromocytomas. It is best for a woman to avoid VHL-related surgery while she is pregnant unless medically necessary. Pregnancy itself does not seem to make VHL worse or make the tumors grow faster, but any tumors that are present should be evaluated, and a plan for surgical removal or monitoring should be in place.

KEY TERMS

Benign—Not cancerous, not able to spread to new places in the body.

Cyst—A fluid filled sac that can be normal or abnormal.

Hemangioblastoma—A benign tumor caused by the abnormal growth of blood vessels.

Malignant—Cancerous, able to spread to new places in the body.

Mutation—A change in the DNA code.

Tumor—An abnormal growth caused by the uncontrolled growth of cells.

See also Cancer genetics; Familial cancer syndrome; Kidney cancer.

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von Recklinghausen's neurofibromatosis

Definition

Von Recklinghausen's neurofibromatosis is also called von Recklinghausen disease, or simply neurofibromatosis (NF)1. It is an automsomal dominant hereditary disorder. NF is the most common neurological disorder caused by a single gene. Patients develop multiple soft tumors (neurofibromas) and very often skin spots (freckling AND café au lait spots). The tumors occur under the skin and throughout the nervous system. The disease is named for Friedrich Daniel von Recklinghausen (1833–1910), a German pathologist, although cases of it have been described in European medical publications since the sixteenth century.

Description

There are three types of neurofibromatosis, although some researchers have proposed as many as eight categories. The two main types of neurofibromatosis are neurofibromatosis 1 (NF1), which affects about 85% of patients diagnosed with neurofibromatosis, and neurofibromatosis 2 (NF2), which accounts for another 10% of patients. NF1 affects approximately 1 in 2,000 to 1 in 5,000 births worldwide. NF2 affects 1 in 35,000 to 1 in 40,000 births worldwide. Recently, schwannomatosis has been recognized as a rare form of NF. Since NF is the most common neurological disorder, NF is more prevalent than the number of people affected by cystic fibrosis, hereditary muscular dystrophy, Huntington's disease, and Tay-Sachs disease combined. In addition to skin and nervous system tumors and skin freckling, NF can lead to disfigurement, blindness, deafness, skeletal abnormalities, loss of limbs, malignancies, and learning disabilities. The degree a person is affected with a form of neurofibromatosis may vary greatly between patients.

Causes and symptoms

A defective gene causes NF1 and NF2. NF1 is due to a defect on chromosome 17q. NF2 results from a defect on chromosome 22. Both neurofibromatosis disorders are inherited in an autosomal dominant fashion. In an autosomal dominant disease, one copy of a defective gene will cause the disease. However, family pattern of NF is only evident for about 50% to 70% of all NF cases. The remaining cases of NF are due to a spontaneous mutation (a change in a person's gene rather than a mutation inherited from a parent). As with an inherited mutated gene, a person with a spontaneously mutated gene has a 50% chance of passing the spontaneously mutated gene to any offspring.

NF1 has a number of possible symptoms:

- Five or more light brown skin spots (café au lait spots, a French term meaning "coffee with milk"). The skin spots measure more than 0.2 inches (5 millimeters) in diameter in patients under the age of puberty or more than 0.6 inches (15 millimeters) in diameter across in adults and children over the age of puberty. Nearly all NF1 patients display café au lait spots.
- Multiple freckles in the armpit or groin area.
- Ninety percent of patients with NF1 have tiny tumors in the iris (colored area of the eye) called Lisch nodules (iris nevi).
- Two or more neurofibromas distributed over the body. Neurofibromas are soft tumors and are the hallmark of NF1. Neurofibromas occur under the skin, often located along nerves or within the gastrointestinal tract. Neurofibromas are small and rubbery, and the skin overlying them may be somewhat purple in color.
- Skeletal deformities, such as a twisted spine (scoliosis), curved spine (humpback), or bowed legs.

- Tumors along the optic nerve, which cause visual disturbances in about 20% of patients.
- The presence of NF1 in a patient's parent, child, or sibling.

There are very high rates of speech impairment, learning disabilities, and attention deficit disorder in children with NF1. Other complications include the development of a seizure disorder, or the abnormal accumulation of fluid within the brain (hydrocephalus). A number of cancers are more common in patients with NF1. These include a variety of types of malignant brain tumors, as well as leukemia, and cancerous tumors of certain muscles (**rhabdomyosarcoma**), the adrenal glands (**pheochromocytoma**), or the kidneys (**Wilms' tumor**). Symptoms are often visible at birth or during infancy, and almost always by the time a child is about 10 years old.

In contrast to patients with NF1, patients with NF2 have few, if any, café au lait spots or tumors under the skin. Patients with NF2 most commonly have tumors (schwannomas) on the eighth cranial nerve (one of 12 pairs of nerves that enter or emerge from the brain), and occasionally on other nerves. The location of the schwann cell derived tumors determines the effect on the body. The characteristic symptoms of NF2 include dysfunction in hearing, ringing in the ears (tinnitus), and body balance. The common characteristic symptoms of NF2 are due to tumors along the acoustic and vestibular branches of the eighth cranial nerve. Tumors that occur on neighboring nervous system structures may cause weakness of the muscles of the face, headache, dizziness, numbness, and weakness in an arm or leg. Cloudy areas on the lens of the eye (called cataracts) frequently develop at an early age. As in NF1, the chance of brain tumors developing is unusually high. Symptoms of NF2 may not begin until after puberty.

Multiple schwannomas on cranial, spinal, and peripheral nerves characterize schwannomatosis. People with schwannomatosis usually have greater problems with pain than with neurological disability. The first symptom of schwannomatosis is usually pain in any part of the body without any source. It can be several years before a tumor is found. About 1/3 of patients with schwannomatosis have tumors in a single part of the body, such as an arm, leg or segment of spine. People with schwannomatosis do not develop vestibular tumors, any other kinds of tumors (such as meningiomas, ependymomas, or astrocytomas), do not go deaf, and do not have learning disabilities.

Diagnosis

Diagnosis of a form of neurofibromatosis is based on the symptoms outlined above. Although a visual inspection may be sufficient for inspection of tumors for a clinical diagnosis of neurofibromatosis, **magnetic resonance imaging** (MRI) is the most useful type of imaging study for early diagnosis of tumors while CT scans are better for detecting skeletal abnormalities. Diagnosis of NF1 requires that at least two of the above listed symptoms are present. A slit lamp is used to visualize the presence of any Lisch nodules in a person's eye. A person with a parent, sibling, or child with NF1 is another tool used to diagnose a person with NF1.

NF2 can be diagnosed three different ways and with symptoms different from NF1 symptoms:

- The presence of bilateral cranial eighth nerve tumors.
- A person who has a parent, sibling, or child with NF2 and a unilateral eighth nerve tumor (vestibular schwannoma or acoustic neuroma).
- A person who has a parent, sibling, or child with NF2 and any two of the following: glioma, **meningioma**, neurofibroma, schwannoma, or an early age cataract.

The presence of multiple schwannomas may be a symptom of NF2 or schwannomatosis. An older person with multiple schwannomas and no hearing loss probably does not have NF2. A high-quality MRI scan should be used to detect any possible vestibular tumors to differentiate between NF2 and schwannomatosis in a younger person with multiple schwannomas or any person with hearing loss and multiple schwannomas.

In prepubertal children a yearly assessment including blood pressure measurement, eye examination, development screening, and neurologic examination is recommended.

Monitoring the progression of neurofibromatosis involves careful testing of vision and hearing (audiometry). X-ray studies of the bones are frequently done to watch for the development of deformities. CT scans and MRI scans are performed to track the development/progression of tumors in the brain and along the nerves. Auditory evoked potentials (the electric response evoked in the cerebral cortex by stimulation of the acoustic nerve) may be helpful to determine involvement of the acoustic nerve, and EEG (electroencephalogram, a record of electrical currents in the brain) may be needed for patients with suspected seizures.

Treatment

There are no cures for any form of neurofibromatosis. To some extent, the symptoms of NF1 and NF2 can be treated individually. Skin tumors can be surgically removed. Some brain tumors, and tumors along the nerves, can be surgically removed, or treated with drugs

KEY TERMS

Audiometry—Testing a person's hearing by exposing ear to sounds in a soundproof room.

Autosomal dominant—Genetic information on a single non-sex chromosome that is expressed with only one copy of a gene. Child of an affected parent has a 50% chance of inheriting an autosomal dominant gene.

Cancer—Abnormal and uncontrolled growth of cells that can invade surrounding tissues and other parts of the body. Although some cancers are treatable, recurrence and death from cancer can occur.

Cataract—Lens of eye loses transparency and becomes cloudy. Cloudiness blocks light rays entering the eye that may lead to blindness.

Chromosome—A structure within the nucleus of every cell, that contains genetic information governing the organism's development. There are 22 non-sex chromosomes and one sex chromosome.

Ependymoma—Tumor that grows from cells that line the cavities of brain ventricles and spinal cord.

Gamma knife—A type of highly focused radiation therapy.

Gene—Piece of information contained on a chromosome. A chromosome is made of many genes.

Magnetic resonance imaging—Magnetic resonance imaging (MRI) measures the response of tissues to magnetic fields to produce detailed pictures of the body, including the brain.

Meningioma—Tumor that grows from the protective brain and spinal cord membrane cells (meninges).

Mutation—A permanent change to the genetic code of an organism. Once established, a mutation can be passed on to offspring.

Neurofibroma—A soft tumor usually located on a nerve.

Radiation therapy—Exposing tumor cells to controlled doses of x-ray irradiation for treatment. Although tumor cells are susceptible to irradiation, surrounding tissues will also be damaged. Radiation therapy alone rarely cures a tumor, but can be useful when used in conjunction with other forms of therapy or when a patient cannot tolerate other forms of therapy.

Schwannoma—Tumor that grows from the cells that line the nerves of the body (Schwann cells).

Tinnitus—Noises in the ear that can include ringing, whistling or booming.

Tumor—An abnormally multiplying mass of cells. Tumors that invade surrounding tissues and other parts of the body are malignant and considered a cancer. Non-malignant tumors do not invade surrounding tissues and other parts of the body. Malignant and non-malignant tumors can cause severe symptoms and death.

(**chemotherapy**) or x-ray treatments (**radiation therapy**, including gamma knife therapy). Twisting or curving of the spine and bowed legs may require surgical treatment or the wearing of a special brace.

Prognosis

Prognosis varies depending on the types of tumors which an individual develops. In general, however, patients with neurofibromatosis have a shortened life expectancy; the average age at death is 55–59 years, compared with 70–74 years for the general United States population. As tumors grow, they begin to destroy surrounding nerves and structures. Ultimately, this destruction can result in blindness, deafness, increasingly poor balance, and increasing difficulty with the coordination necessary for walking. Deformities of the bones and spine can also interfere with walking and movement. When cancers develop, prognosis worsens according to the specific type of cancer.

Clinical Trials

As of 2004 the National Cancer Institute (NCI) is sponsoring one clinical trial for children with neurofibromatosis type 1. The trial is an evaluation of tipifarnib (Zarnestra), a drug that inactivates certain proteins that encourage tumor growth. It is hoped that tipifarnib may prove to be an effective drug treatment for the disorder, as surgery is presently considered the only standard treatment.

The use of an auditory brainstem implant (ABI) as part of hearing rehabilitation in patients with NF2 has been tested in Europe and the United States.

Prevention

There is no known way to prevent the cases of NF that are due to a spontaneous change in the genes (mutation). Since genetic tests for NF1 and NF2 are available,

QUESTIONS TO ASK THE DOCTOR

- How can I tell if I have neurofibromatosis?
- Which type of neurofibromatosis do I have?
- Will I develop tumors? Will they be cancerous?
- Is my neurofibromatosis genetic?
- What medical tests are important?
- What treatments are available for neurofibromatosis?
- Will I die from neurofibromatosis?

new cases of inherited NF can be prevented with careful genetic counseling. A person with NF can be made to understand that each of his or her offspring has a 50% chance of also having NF. When a parent has NF, and the specific genetic defect causing the parent's disease has been identified, prenatal tests can be performed on the fetus during pregnancy. Amniocentesis and chorionic villus sampling are two techniques that allow small amounts of the baby's cells to be removed for examination. The tissue can then be examined for the presence of the parent's genetic defect. Some families choose to use this information in order to prepare for the arrival of a child with a serious medical problem. Other families may choose not to continue the pregnancy. **Genetic testing** may also be useful for evaluating individuals with a family history of neurofibromatosis, who do not yet show symptoms.

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March of Dimes Birth Defects Foundation. National Office, 1275 Mamaroneck Ave., White Plains, NY 10605. <http://www.modimes.org>.

Massachusetts General Hospital Neurofibromatosis Clinic. Harvard Medical School, Massachusetts General Hospital, Boston, MA 02114. (617) 724-7856. <http://neurosurgery.mgh.harvard.edu/NFclinic.htm>.

National Cancer Institute. Information Office, Building 31, Room 10A03, 9000 Rockville Pike, Bethesda, MD, 20892-2580. (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

National Institute of Child Health and Human Development. Building 31, Room 2A32, MSC 2425, 31 Center Dr., Bethesda, MD, 20892. (800) 370-2943. <http://www.nichd.nih.gov>.

National Institute of Neurological Disorders and Stroke. Office of Communications and Public Liaison, PO Box 5801, Bethesda, MD, 20824. (800) 352-9424. <http://www.ninds.nih.gov>. National Organization focused on neurological biomedical research.

The National Neurofibromatosis Foundation, Inc.(NNF). 95 Pine St., 16th Floor, New York, NY 10005. (800) 323-7938. <http://www.nf.org>.

Neurofibromatosis Association (NFA). 82 London Road, Kingston upon Thames, Surrey KT2 6PX. 0208 547 1636. e-mail: nfa@zetnet.co.uk. <http://www.nfa.zetnet.co.uk>.

Neurofibromatosis, Inc. 8855 Annapolis Rd., #110, Lanham, MD 20706-2924. (800) 942-6825. <http://www.nfinc.org>.

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Vulvar cancer

Definition

Vulvar cancer refers to an abnormal, cancerous growth in the external female genitalia.

Description

Vulvar cancer is a rare disease that occurs mainly in elderly women. The vulva refers to the external female genitalia, which includes the labia, the opening of the vagina, the clitoris, and the space between the vagina and anus (perineum). There are two pairs of labia (a Latin term meaning lips). The labia meet to protect the openings of the vagina and the tube that connects to the bladder (urethra). The outer, most prominent folds of skin are called labia majora, and the smaller, inner skin folds are called labia minora. Vulvar cancer can affect any part of the female genitalia, but usually affects the labia.

Approximately 70% of vulvar cancers involve the labia (usually the labia majora), 15% to 20% involve the clitoris, and 15% to 20% involve the perineum. For approximately 5% of the cases, the cancer is present at more than one location. For approximately 10% of the cases, so much of the vulva is affected by cancer that the original location cannot be determined. Vulvar cancer can spread to nearby structures including the anus, vagina, and urethra.

Most vulvar cancers are squamous cell carcinomas. Squamous cells are the main cell type of the skin. Squamous cell **carcinoma** often begins at the edges of the labia majora or labia minora or the area around the vagina. This type of cancer is usually slow-growing and may begin with a precancerous condition referred to as vulvar intraepithelial neoplasia (VIN), or dysplasia. This means that precancerous cells are present in the surface layer of skin.

Other, less common types of vulvar cancer are **melanoma**, **basal cell carcinoma**, **adenocarcinomas**, Paget's disease of the vulva, and tumors of the connective tissue under the skin. Melanoma, a cancer that develops from the cells that produce the pigment that determines the skin's color, can occur anywhere on the skin, including the vulva. Melanoma is the second most common type of vulvar cancer, and accounts for 5% to 10% of the cases. Half of all vulvar melanomas involve the labia majora. Basal cell carcinoma, which is the most common type of cancer that occurs on parts of the skin exposed to the sun, very rarely occurs on the vulva. Adenocarcinomas develop from glands, including the glands at the opening of the vagina (Bartholin's glands) that produce a mucus-like lubricating fluid.

Vulvar cancer is most common in women over 50 years of age. The median age at diagnosis is 65 to 70 years old. Additional risk factors for vulvar cancer include having multiple sexual partners, **cervical cancer**, and the presence of chronic vaginal and vulvar inflammations. This type of cancer is often associated with sexually transmitted diseases.

Demographics

Vulvar cancer is most common in women who are between the ages of 65 and 75 years. In the United States there are approximately 3,000 new cases of vulvar cancer diagnosed each year. Vulvar cancer accounts for only 1% of all cancers in women. Approximately 5% of all **gynecologic cancers** occur on the vulva. For unknown reasons, the incidence of vulvar cancer seems to be rising.

Causes and symptoms

Cancer is caused when the normal mechanisms that control cell growth become disturbed, causing the cells to grow continually without stopping. This is usually the result of damage to the DNA in the cell. Although the cause of vulvar cancer is unknown, studies have identified several risk factors for vulvar cancer. These include:

- Vulvar intraepithelial neoplasia (VIN). This abnormal growth of the surface cells of the vulva can sometimes progress to cancer.
- Infection with human papillomavirus (HPV). This virus is sexually transmitted and can cause genital warts. Although HPV DNA can be detected in most cases of vulvar intraepithelial neoplasia, it is detected in fewer than half of all cases of vulvar cancer. Therefore, the link between HPV infection and vulvar cancer is unclear. As of 2001, it is theorized that two classes of vulvar cancer exist: one that is associated with HPV infection and one that is not.
- Herpes simplex virus 2 (HSV2). This sexually transmitted virus is also associated with increased risk for vulvar cancer.
- Cigarette smoking. Smoking in combination with infection by HPV or HSV2 was found to be a particularly strong risk factor for vulvar cancer.
- Infection with human immunodeficiency virus (HIV). This virus, which causes AIDS, decreases the body's immune ability, leaving it vulnerable to a variety of diseases, including vulvar cancer.
- Chronic vulvar inflammation. Long-term irritation and inflammation of the vulva and vagina, which may be caused by poor hygiene, can increase the risk of vulvar cancer.

- Abnormal Pap smears. Women who have had abnormal Pap smears are at an increased risk of developing vulvar cancer.
- Chronic immunosuppression. Women who have had long-term suppression of their immune system caused by disease (such as certain cancers) or medication (such as those taken after organ transplantation) have an increased risk of developing vulvar cancer.

The hallmark symptom of vulvar cancer is **itching** (pruritus), which is experienced by 90% of the women afflicted by this cancer. The cancerous lesion is readily visible. Unfortunately, because of embarrassment or denial, it is not uncommon for women to delay medical assessment of vulvar abnormalities. Any abnormalities should be reported to a gynecologist.

If squamous cell vulvar cancer is present, it may appear as a raised red, pink, or white bump (nodule). It is often accompanied by pain, bleeding, vaginal discharge, and painful urination. Malignant melanoma of the vulva usually appears as a pigmented, ulcerated growth. Other types of vulvar cancer may appear as a distinct mass of tissue, sore and scaly areas, or cauliflower-like growths that look like warts.

Diagnosis

A gynecological examination will be used to observe the suspected area. During this examination, the physician may use a special magnifying instrument called a colposcope to view the area better. Additionally, the area may be treated with a dilute solution of acetic acid, which causes some abnormal areas to turn white, making them easier to see. During this examination, if any area is suspected of being abnormal, a tissue sample (**biopsy**) will be taken. The biopsy can be performed in the doctor's office with the use of local anesthetic. A wedge-shaped piece of tissue, which contains the suspect lesion with some surrounding normal skin and the underlying skin layers and connective tissue, will be removed. Small lesions will be removed in their entirety (excisional biopsy). The diagnosis of cancer depends on a microscopic analysis of this tissue by a pathologist.

The diagnosis for vulvar cancer will determine how advanced the cancer is and how much it has spread. This is determined by the size of the tumor and how deep it has invaded the surrounding tissue and organs, such as the lymph nodes. It will also be determined if the cancer has metastasized, or spread to other organs. Tests used to determine the extent of the cancer include **x ray** and **computed tomography** scan (CT scan). Endoscopic examination of the bladder (**cystoscopy**) and/or rectum (proctoscopy) may be performed if it is suspected that the cancer has spread to these organs.

Treatment team

The treatment team for vulvar cancer may include a gynecologist, gynecologic oncologist, radiation oncologist, gynecologic nurse oncologist, sexual therapist, psychiatrist, psychological counselor, and social worker.

Clinical staging, treatments, and prognosis

Clinical staging

The International Federation of Gynecology and Obstetrics (FIGO) has adopted a surgical staging system for vulvar cancer. The stage of cancer is determined after surgery. The previous clinical staging system for vulvar cancer is no longer used. Vulvar cancer is categorized into five stages (0, I, II, III, and IV) which may be further subdivided (A and B) based on the depth or spread of cancerous tissue. The FIGO stages for vulvar cancer are:

- Stage 0. Vulvar intraepithelial neoplasia (precancerous cells).
- Stage I. Cancer is confined to the vulva and perineum. The lesion is less than 2 cm (about 0.8 in) in size.
- Stage II. Cancer is confined to the vulva and perineum. The lesion is larger than 2 cm (larger than 0.8 in) in size.
- Stage III. Cancer has spread to the vagina, urethra, anus, and/or the lymph nodes in the groin (inguinofemoral).
- Stage IV. Cancer has spread to the bladder, bowel, pelvic bone, pelvic lymph nodes, and/or other parts of the body.

Treatments

Treatment for vulvar cancer will depend on its stage and the patient's general state of health. Surgery is the mainstay of treatment for most cases of vulvar cancer.

SURGERY The primary treatment for stage I and stage II vulvar cancer is surgery to remove the cancerous lesion and possibly the inguinofemoral lymph nodes. Removal of the lesion may be done by laser, to burn off a minimal amount of tissue, or by scalpel (local excision), to remove more of the tissue. The choice will depend on the severity of the cancer. If a large area of the vulva is removed, it is called a vulvectomy. Radical vulvectomy removes the entire vulva. A vulvectomy may require skin grafts from other areas of the body to cover the wound and make an artificial vulva. Because of the significant morbidity and the psychosexual consequences of radical vulvectomy, there is a trend toward minimizing the extent of cancer excision. The specific inguinofemoral lymph node that would receive lymph fluid from the cancerous lesion, known as the sentinel node, may be

exposed for examination (**lymph node dissection**) or removed (lymphadenectomy), especially in cases in which the cancerous lesion has invaded to a depth of more than 1 mm. Surgery may also be followed by **chemotherapy** and/or **radiation therapy** to kill additional cancer cells.

Surgical treatment of stage III and stage IV vulvar cancer is much more complex. Extensive surgery would be necessary to completely remove the cancerous tissue. Surgery would involve excision of pelvic organs (pelvic **exenteration**), radical vulvectomy, and lymphadenectomy. Because this extensive surgery comes with a substantial risk of complications, it may be possible to treat advanced vulvar cancer with minimal surgery by using radiation therapy and/or chemotherapy as additional treatment (adjuvant therapy).

An intraoperative technique that is used to identify the sentinel node in **breast cancer** and melanoma is being applied to vulvar cancer. This technique, called lymphoscintigraphy, is performed during surgical treatment of vulvar cancer and allows the surgeon to immediately identify the sentinel node. A radioactive compound (technetium 99m sulfur colloid) is injected into the cancerous lesion approximately two hours prior to surgery. This injection causes little discomfort, so local anesthesia is not required. During surgery, a radioactivity detector is used to locate the sentinel node and any other nodes to which cancer has spread. Though still in the experimental stage, vulvar lymphoscintigraphy shows promise in reducing morbidity and hospital length of stay.

The most common complication of vulvectomy is the development of a tumor-like collection of clear liquid (wound seroma). Other surgical complications include urinary tract infection, wound infection, temporary nerve injury, fluid accumulation (edema) in the legs, urinary **incontinence**, falling or sinking of the genitals (genital prolapse), and blood clots (thrombus).

RADIATION THERAPY Radiation therapy uses high-energy radiation from x rays and gamma rays to kill the cancer cells. The skin in the treated area may become red and dry and may take as long as a year to return to normal. **Fatigue**, upset stomach, **diarrhea**, and nausea are also common complaints of women having radiation therapy. Radiation therapy in the pelvic area may cause the vagina to become narrow as scar tissue forms. This phenomenon, known as vaginal stenosis, makes intercourse painful.

CHEMOTHERAPY Chemotherapy uses anticancer drugs to kill the cancer cells. The drugs are given by mouth (orally) or intravenously. They enter the bloodstream and can travel to all parts of the body to kill cancer cells. Generally, a combination of drugs is given because it is more effective than a single drug in treating cancer. The side effects of chemotherapy are significant and include stomach upset, vomiting, appetite loss (anorexia), hair loss (alopecia), mouth or vaginal sores, fatigue, menstrual cycle changes, and premature menopause. There is also an increased chance of infections.

Prognosis

Factors that are correlated with disease outcome include the diameter and depth of the cancerous lesion, involvement of local lymph nodes, cell type, HPV status, and age of the patient. Vulvar cancers that are HPV positive have a better prognosis than those that are HPV negative. The 5-year survival rate is 98% for stage I vulvar cancer and 87% for stage II vulvar cancer. The survival rate drops steadily as the number of affected lymph nodes increases. The survival rate is 75% for patients with one or two, 36% for those with three or four, and 24% for those with five or six involved lymph nodes. The previous statistics were obtained from studies of patients who received surgical treatment only and cannot be used to determine survival rates when adjuvant therapy is employed.

Vulvar cancer can spread locally to encompass the anus, vagina, and urethra. Because of the anatomy of the vulva, it is not uncommon for the cancer to spread to the local lymph nodes. Advanced stages of vulvar cancer can affect the pelvic bone. The lungs are the most common site for vulvar cancer **metastasis**. Metastasis through the blood (hematogenous spread) is uncommon.

Alternative and complementary therapies

Although alternative and complementary therapies are used by many cancer patients, very few controlled studies on the effectiveness of such therapies exist. Mind-body techniques such as prayer, biofeedback, visualization, meditation, and yoga have not shown any effect in reducing cancer but can reduce stress and lessen some of the side effects of cancer treatments. Clinical studies of hydrazine sulfate found that it had no effect on cancer and even worsened the health and well- being of the study subjects. One clinical study of the drug amygdalin (Laetrile) found that it had no effect on cancer. Laetrile can be toxic and has caused death. Shark cartilage, although highly touted as an effective cancer treatment, is an improbable therapy that has not been the subject of clinical study.

The American Cancer Society has found that the ''metabolic diets'' pose serious risk to the patient. The effectiveness of the macrobiotic, Gerson, and Kelley diets and the Manner metabolic therapy has not been

scientifically proven. The FDA was unable to substantiate the anticancer claims made about the popular Cancell treatment.

There is no evidence for the effectiveness of most over-the-counter herbal cancer remedies. However, some herbals have shown an anticancer effect. As shown in clinical studies, Polysaccharide krestin, from the mushroom *Coriolus versicolor*, has significant effectiveness against cancer. In a small study, the green alga *Chlorella pyrenoidosa* has been shown to have anticancer activity. In a few small studies, evening primrose oil has shown some benefit in the treatment of cancer. Patients should discuss the use of any alternative or complementary therapies with their doctor.

For more comprehensive information, the patient should consult the book on complementary and alternative medicine published by the American Cancer Society listed in the Resources section.

Coping with cancer treatment

The patient should consult her treatment team regarding any side effects or complications of treatment. Vaginal stenosis can be prevented and treated by vaginal dilators, gentle douching, and sexual intercourse. A water-soluble lubricant may be used to make sexual intercourse more comfortable. Many of the side effects of chemotherapy can be relieved by medications. Women should consult a psychotherapist and/or join a support group to deal with the emotional consequences of cancer and vulvectomy.

Clinical trials

There are some active, long-term **clinical trials** for the diagnosis and treatment of vulvar cancer. Two of these trials are sponsored by the National Cancer Institute. One trial (protocol ID# GOG-173) is testing the effectiveness of a **sentinel lymph node mapping** technique which uses a visible dye. The sentinel node is identified and removed. This diagnostic and treatment study is open to patients with invasive squamous cell carcinoma of the vulva. The other trial (protocol ID# GOG-0185) is testing the effectiveness of the chemotherapeutic agent **cisplatin** in combination with radiation therapy. This treatment study is open to patients with stage I, II, or III squamous cell carcinoma of the vulva. Women should consult with their treatment team to determine if they are candidates for these or any other clinical studies.

Prevention

The risk of vulvar cancer can be decreased by avoiding risk factors, most of which involve lifestyle choices.

KEY TERMS

Adjuvant therapy—A treatment that is intended to aid primary treatment. Adjuvant treatments for vulvar cancer are radiation therapy and chemotherapy.

Biopsy—Removal of a small piece of tissue for microscopic examination. This is done under local anesthesia and removed by either using a scalpel or a punch, which removes a small cylindrical portion of tissue.

Colposcope—An instrument used for examination of the vagina and cervix. Part of the instrument includes a magnifying lens for better visualization.

Metastasis—The movement of cancer cells from one area of the body to another. This occurs through the blood vessels or the lymph vessels.

Pelvic exenteration—Surgical removal of the organs of the true pelvis which includes the uterus, vagina, and cervix.

Sentinel lymph node—The first lymph node to receive lymph fluid from a tumor. If the sentinel node is cancer-free, then it is likely that the cancerous cells have not metastasized.

Specifically, to reduce the risk of vulvar cancer, women should not smoke and should refrain from engaging in unsafe sexual behavior. Good hygiene of the genital area to prevent infection and inflammation may also reduce the risk of vulvar cancer.

Because vulvar cancer is highly curable in its early stages, women should consult a physician as soon as a vulvar abnormality is detected. Regular gynecological examinations are necessary to detect precancerous conditions that can be treated before the cancer becomes invasive. Because some vulvar cancer is a type of skin cancer, the American Cancer Society also recommends self-examination of the vulva using a mirror. If moles are present in the genital area, women should employ the ABCD rule:

- Asymmetry. A cancerous mole may have two halves of unequal size.
- Border irregularity. A cancerous mole may have ragged or notched edges.
- Color. A cancerous mole may have variations in color.
- Diameter. A cancerous mole may have a diameter wider than 6 mm (1/4 in).

QUESTIONS TO ASK THE DOCTOR

- What type of cancer do I have?
- What stage of cancer do I have?
- What is the five-year survival rate for women with this type and stage of cancer?
- Has the cancer spread?
- What are my treatment options?
- How much tissue will you be removing? Can you remove less tissue and complement my treatment with adjuvant therapy?
- What are the risks and side effects of these treatments?
- What medications can I take to relieve treatment side effects?
- Are there any clinical studies underway that would be appropriate for me?
- What effective alternative or complementary treatments are available for this type of cancer?
- How debilitating is the treatment? Will I be able to continue working?
- How will the treatment affect my sexuality?
- Are there any restrictions regarding sexual activity?
- How realistic will a vulvar reconstruction look?
- Are there any local support groups for vulvar cancer patients?
- What is the chance that the cancer will recur?
- Is there anything I can do to prevent recurrence?
- How often will I have follow-up examinations?

Special concerns

Surgical removal of the cancerous lesion may remove some or all of the vulva. Vulvectomy alters the appearance of the vulva and affects sexual function. **Depression**, due to the effects of surgery on appearance and **sexuality**, may occur. Short-term and long-term complications following extensive surgical treatment of vulvar cancer are not uncommon. Women of child-bearing age should discuss future fertility with their physician.

Resources

BOOKS

Bruss, Katherine, Christina Salter, and Esmeralda Galan, editors. *American Cancer Society's Guide to Complementary and Alternative Cancer Methods*. Atlanta: American Cancer Society, 2000.

Eifel, Patricia, Jonathan Berrek, and James Thigpen. "Cancer of the Cervix, Vagina, and Vulva." In *Cancer: Principles & Practice of Oncology*, edited by Vincent DeVita, Samuel Hellman, and Steven Rosenberg. Philadelphia: Lippincott Williams & Wilkins, 2001.

Garcia, Agustin, and J. Tate Thigpen. "Tumors of the Vulva and Vagina." In *Textbook of Uncommon Cancer*, edited by D. Raghavan, M. Brecher, D. Johnson, N. Meropol, P. Moots, and J. Thigpen. Chichester: John Wiley & Sons, 1999.

Primack, Aron. "Complementary/Alternative Therapies in the Prevention and Treatment of Cancer." In *Complementary/Alternative Medicine: An Evidence-Based Approach*, edited by John Spencer and Joseph Jacobs. St. Louis: Mosby, 1999.

PERIODICALS

Grendys, Edward, and James Fiorica. "Innovations in the Management of Vulvar Carcinoma." *Current Opinion in Obstetrics and Gynecology* 12 (February 2000): 15-20.

ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) ACS-2345. <http://www.cancer.org>.

Cancer Research Institute, National Headquarters. 681 Fifth Ave., New York, NY 10022. (800) 992-2623. <http://www.cancerresearch.org>.

Gynecologic Cancer Foundation. 401 N. Michigan Ave., Chicago, IL 60611. (800) 444-4441 or (312) 644-6610. <http://www.wcn.org/gcf>.

National Institutes of Health. National Cancer Institute. 9000 Rockville Pike, Bethesda, MD 20982. (800) 4-CANCER. <http://cancernet.nci.nih.gov>.

OTHER

Cancer Care News. [cited July 3, 2001]. <http://www.cancercare.org>.

Quackwatch, Questionable Cancer Therapies. [cited July 3, 2001]. <http://www.quackwatch.com>.

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W

Waldenström's macroglobulinemia

Definition

Waldenström's macroglobulinemia is a rare, chronic cancer of the immune system that is characterized by hyperviscosity, or thickening, of the blood.

Description

Waldenström's (Waldenström, Waldenstroem's) macroglobulinemia (WM) is a lymphoma, or cancer of the lymphatic system. It was first identified in 1944, by the Swedish physician Jan Gosta Waldenström, in patients who had a thickening of the serum, or liquid part, of the blood. Their blood serum contained a great deal of a very large molecule called a globulin. Thus, the disorder is called macroglobulinemia.

Lymphomas are cancers that originate in tissues of the lymphatic system. All lymphomas other than **Hodgkin's disease**, including WM, are known collectively as **non-Hodgkin's lymphomas**. There are 13 major types of non-Hodgkin's lymphomas, and others that are very rare. Other names that are sometimes used for WM include: lymphoplasmacytic lymphoma, lymphoplasmacytic leukemia, macroglobulinemia of Waldenström, primary macroglobulinemia, Waldenström's syndrome, Waldenström's purpura, or hyperglobulinemic purpura. Purpura refers to purple spots on the skin, resulting from the frequent bleeding and bruising that can be a symptom of WM.

WM is classified as a low-grade or indolent form of lymphoma because it is a slow-growing cancer that produces fewer symptoms than other types of lymphomas. WM most often affects males over the age of 65. Frequently, this disease produces no symptoms and does not require treatment. It has not been studied as extensively as other types of lymphoma.

The lymphatic system

The lymphatic system is part of the body's immune system, for fighting disease, and part of the blood-producing system. It includes the lymph vessels and nodes, and the spleen, bone marrow, and thymus. The narrow lymphatic vessels carry lymphatic fluid from throughout the body. The lymph nodes are small, pea-shaped organs that filter the lymphatic fluid and trap foreign substances, including viruses, bacteria, and cancer cells. The spleen, in the upper left abdomen, removes old cells and debris from the blood. The bone marrow, the spongy tissue inside the bones, produces new blood cells.

B lymphocytes or B cells are white blood cells that recognize disease-causing organisms. They circulate throughout the body in the blood and lymphatic fluid. Each B lymphocyte recognizes a specific foreign substance, or antigen. When it encounters its specific antigen, the B cell begins to divide and multiply, producing large numbers of identical (monoclonal), mature plasma cells. These plasma cells produce large amounts of antibody that are specific for the antigen. Antibodies are large proteins called immunoglobulins (Igs) that bind to and remove the specific antigen.

A type of Ig, called IgM, is part of the early **immune response**. The IgM molecules form clusters in the bloodstream. When these IgM clusters encounter their specific antigen, usually a bacterium, they cover it so that it can be destroyed by other immune system cells.

Plasma cell neoplasm

WM is a type of plasma cell neoplasm or B-cell lymphoma. These are lymphomas in which certain plasma cells become abnormal, or cancerous, and begin to grow uncontrollably. In WM, the cancerous plasma cells overproduce large amounts of identical (monoclonal) IgM antibody. This IgM also is called M protein, for monoclonal or **myeloma** protein.

Macroglobulinemia refers to the accumulation of this M protein in the serum of the blood. This large amount of M protein can cause the blood to thicken, causing hyperviscosity. The malignant plasma cells of some WM patients also produce and secrete partial immunoglobulins called light chains, or Bence-Jones proteins. The malignant plasma cells can invade various tissues, including the bone marrow, lymph nodes, and spleen, causing these tissues to swell.

Demographics

WM accounts for about 1-2% of non-Hodgkin's lymphomas. It is estimated that it may affect about five out of every 100,000 people. It usually affects people over the age of 50, and most often develops after age 65. It is more common in men than in women. In the United States, WM is more common among Caucasians than among African Americans. The disease can run in families.

Causes and symptoms

The cause of WM is not known.

Many individuals with WM have no symptoms of the disease. This is known as asymptomatic macroglobulinemia. When symptoms of WM are present, they may vary greatly from one individual to the next.

Hyperviscosity syndrome

At least 50% of individuals with WM have hyperviscosity syndrome, an increased viscosity or thickening of the blood caused by the accumulation of IgM in the serum. Hyperviscosity can cause a slowing in the circulation through small blood vessels. This condition can lead to a variety of symptoms:

- **fatigue**
- weakness
- rash
- bruising
- nose bleeds
- gastrointestinal bleeding
- weight loss
- night sweats
- increased and recurrent infections
- poor blood circulation in the extremitiesPoor blood circulation, or Raynaud's phenomenon, can affect any part of the body, but particularly the fingers, toes, nose, and ears.

Cold weather can cause additional circulatory problems, by further thickening the blood and slowing down circulation. In some cases, the excess blood protein may precipitate out of the blood in the cold, creating particles that can block small blood vessels. This is called cryoglobulinemia. The extremities may turn white, or a patchy red and white. The hands, feet, fingers, toes, ears, and nose may feel cold, numb, or painful.

Hyperviscosity may affect the brain and nervous system, leading to additional symptoms. These symptoms include:

- peripheral **neuropathy**, caused by changes in the nerves, leading to pain or numbness in the extremities
- dizziness
- headaches
- vision problems or loss of vision
- mental confusion
- poor coordination
- temporary paralysis
- mental changes

Hyperviscosity can clog the tubules that form the filtering system of the kidneys, leading to kidney damage or kidney failure. Existing heart conditions can be aggravated by WM. In extreme cases, WM may result in heart failure. Late-stage WM also may lead to mental changes that can progress to coma.

Anemia

The accumulation of IgM in the blood causes an increase in the volume of the blood plasma. This effectively dilutes out the red blood cells and other blood components. The lowered concentration of red blood cells can lead to **anemia** and cause serious fatigue. Likewise, a deficiency in platelets (**thrombocytopenia**), which cause the blood to clot, can result in easy bleeding and bruising. As the cancer progresses, there may be abnormal bleeding from the gums, nose, mouth, and intestinal tract. There may be bluish discoloration of the skin. In the later stages of the disease, leukopenia, a deficiency in white blood cells, also can develop.

Organ involvement

In 5-10% of WM cases, the IgM may be deposited in tissues. Thus, some individuals with WM have enlargement of the lymph nodes, the spleen, and/or the liver.

If Bence-Jones proteins are produced by the malignant plasma cells, they may be deposited in the kidneys. There they can plug up the tiny tubules that form the filtering system of the kidneys. This can lead to kidney damage and kidney failure.

Diagnosis

Since many individuals with WM have no symptoms, the initial diagnosis may result from blood tests that are performed for some other purpose. Blood cell counts may reveal low red blood cell and platelet levels. A physical examination may indicate enlargement of the lymph nodes, spleen, and/or liver. A retinal eye examination with an ophthalmoscope may show retinal veins that are enlarged or bleeding.

Blood and urine tests

Serum **protein electrophoresis** is used to measure proteins in the blood. In this laboratory procedure, serum proteins are separated in an electrical field, based on the size and electrical charge of the proteins. Serum **immunoelectrophoresis** uses a second antibody that reacts with IgM. A spike in the Ig fraction indicates a large amount of identical or monoclonal IgM in individuals with WM.

Normal serum contains 0.7-1.6 gm per deciliter (g/dl) of Ig, with no monoclonal Ig present. At serum IgM concentrations of 3-5 g/dl, symptoms of hyperviscosity often are present. However some individuals remain asymptomatic with IgM levels as high as 9 g/dl.

Urinalysis may indicate protein in the urine. A urine Bence-Jones protein test may indicate the presence of these small, partial Igs.

Bone marrow

Abnormal blood tests usually are followed by a bone marrow **biopsy**. In this procedure, a needle is inserted into a bone and a small amount of marrow is removed. Microscopic examination of the marrow may reveal elevated levels of lymphocytes and plasma cells. However, less than 5% of patients with WM have lytic bone lesions, caused by cancerous plasma cells in the bone marrow that are destroying healthy cells. Bone lesions can be detected with x rays.

Treatment team

WM usually is diagnosed and treated by a hematologist/oncologist, a specialist in diseases of the blood. Asymptomatic macroglobulinemia is followed closely by the patient's physician for the development of symptoms.

Clinical staging, treatments, and prognosis

Clinical staging, to define how far a cancer has spread through the body, is the common method for choosing a cancer treatment. However, there is no generally accepted staging system for WM.

There also is no generally accepted course of treatment for WM. Treatment may not be necessary for asymptomatic macroglobulinemia. However, if IgM serum levels are very high, treatment may be initiated even in the absence of symptoms. If symptoms are present, treatment is directed at relieving symptoms and retarding the disease's development. Of major concern is the prevention or alleviation of blood hyperviscosity. Therefore, the initial treatment depends on the viscosity of the blood at diagnosis.

Hyperviscosity

Plasmapheresis, or plasma exchange transfusion, is a procedure for thinning the blood. In this treatment, blood is removed and passed through a cell separator that removes the plasma, containing the IgM, from the red and white blood cells and platelets. The blood cells are transfused back into the patient, along with a plasma substitute or donated plasma. Plasmapheresis relieves many of the acute symptoms of WM. Individuals with WM may be given fluid to counter the effects of hyperviscous blood.

Low blood cell counts

Treatments for low blood cell levels include:

- the drug Procrit to treat anemia
- transfusions with packed red blood cells to treat anemia in later stages of the disease
- antibiotics to treat infections caused by a deficiency in white blood cells
- transfusions with blood platelets

Chemotherapy

Chemotherapy, the use of anti-cancer drugs, helps to slow the abnormal development of plasma cells, but does not cure WM. It can reduce the amount of IgM in the bone marrow. In particular, chemotherapy is used to treat severe hyperviscosity and anemia that are caused by WM.

Chlorambucil (Leukeran), possibly in combination with prednisone, is the typical chemotherapy choice for WM. This treatment is effective in 57% of cases. These drugs are taken by mouth. Prednisone is a corticosteroid that affects many body systems. It has anti-cancer and anti-inflammatory effects and is an immune system suppressant. Other drug combinations that are used to treat WM include **cyclophosphamide** (Cytoxan), **vincristine**, and prednisone, with or without **doxorubicin**. Fludarabine, 2-chlorodeoxyadenosine, and **corticosteroids** also may be used.

KEY TERMS

Anemia—Any condition in which the red blood cell count is below normal.

Antibody—Immunoglobulin produced by immune system cells that recognizes and binds to a specific foreign substance (antigen).

Antigen—Foreign substance that is recognized by a specific antibody.

Autosomal dominant—Genetic trait that is expressed when present on only one of a pair of non-sex-linked chromosomes.

B cell (B lymphocyte)—Type of white blood cell that produces antibodies.

Bence-Jones protein—Light chain of an immunoglobulin that may be overproduced in Waldenström's macroglobulinemia; it is excreted in the urine.

Biopsy—Removal of a small sample of tissue for examination under a microscope; used in the diagnosis of cancer.

Cryoglobulinemia—Condition in which protein in the blood forms particles in the cold, blocking blood vessels and leading to pain and numbness of the extremities.

Hyperviscosity—Thick, viscous blood, caused by the accumulation of large proteins, such as immunoglobulins, in the serum.

Immunoelectrophoresis—Use of an electrical field to separate proteins in a mixture (such as blood or urine), on the basis of the size and electrical charge of the proteins; followed by the detection of an antigen (such as IgM), using a specific antibody.

Immunoglobulin (Ig)—Antibody such as IgM; large protein produced by B cells that recognizes and binds to a specific antigen.

Interferon alpha—Potent immune-defense protein; used as an anti-cancer drug.

Lymphatic system—The vessels, lymph nodes, and organs, including the bone marrow, spleen, and thymus, that produce and carry white blood cells to fight disease.

Lymphoma—Cancer that originates in lymphatic tissue.

M protein—Monoclonal or myeloma protein; IgM that is overproduced in Waldenström's macroglobulinemia and accumulates in the blood and urine.

Monoclonal—Identical cells or proteins; cells (clones) derived from a single, genetically distinct cell, or proteins produced by these cells.

Plasma cell—Type of white blood cell that produces antibodies; derived from an antigen-specific B cell.

Plasmapheresis—Plasma exchange transfusion; the separation of serum from blood cells to treat hyperviscosity of the blood.

Platelet—Cell that is involved in blood clotting.

Stem cell—Undifferentiated cell that retains the ability to develop into any one of numerous cell types.

Side effects of chemotherapy may include:

- Mouth sores
- Nausea and indigestion
- Hair loss (alopecia)
- Increased appetite
- Nervousness
- Insomnia These side effects disappear after the chemotherapy is discontinued.

The long-term management of WM usually is accomplished through a combination of plasmapheresis and chemotherapy.

Alternative and complementary therapies

Biological therapy or immunotherapy, with the potent, immune system protein interferon alpha, is used to relieve the symptoms of WM. Interferon alpha works by boosting the body's immune response. Interferon can cause flu-like symptoms, such as **fever**, chills, and fatigue. It also can cause digestive problems and may affect blood pressure.

The drug **rituximab**, an antibody that is active against antibody-producing cells, is effective in about 30% of individuals with WM. Rituximab is a monoclonal antibody produced in the laboratory. Monoclonal antibody treatment may cause a an allergic reaction in some people.

Prognosis

There is no cure for WM. In general, patients go into partial or complete remission following initial treatments. However the disease is not cured and follow-up treatment may be necessary.

QUESTIONS TO ASK THE DOCTOR

- Why have you diagnosed Waldenström's macroglobulinemia?
- Is my disease likely to progress?
- Do you recommend treatment, and if so, why?
- What are my treatment options?
- What is my prognosis?

The prognosis for this cancer depends on an individual's age, general health, and genetic (hereditary) makeup. Males, individuals over age 60, and those with severe anemia have the lowest survival rates. The Revised European American Lymphoma (REAL) classification system gives WM a good prognosis following treatment, with an average five-year survival rate of 50-70%. However, many people with WM live much longer, some without developing any symptoms of the disease. About 16-23% of individuals with WM die of unrelated causes.

Clinical trials

Clinical studies for the treatment of WM are ongoing. These studies are focusing on new anti-cancer drugs, new combinations of drugs for chemotherapy, and new biological therapies to boost the immune system. The drug **thalidomide** is a promising new treatment for WM. Its mode of action is unclear; the drug appears to have various effects on the immune system and may inhibit cancerous plasma cells, both directly and indirectly. If thalidomide is taken during pregnancy, it can cause severe birth defects or death of the fetus.

Biological therapies in clinical trial include **monoclonal antibodies** that contain radioactive substances (radioimmunotherapy), in combination with autologous peripheral blood stem cell rescue or transplantation (PBSCT). With PBSCT, the patient's peripheral blood stem cells (immature bone marrow cells found in the blood) are collected and frozen prior to radioimmunotherapy, which destroys bone marrow cells. A procedure called apheresis is used to collect the stem cells. Following the therapy, the stem cells are reinjected into the individual. The procedure is autologous because it utilizes the individual's own cells. A similar procedure that utilizes chemotherapy with PBSCT also is being tested.

Prevention

There is no known prevention for WM.

Special concerns

WM is a rare disorder and many physicians and even hematologists may not have had experience with it. Furthermore, there is not a clear consensus among professionals as to what constitutes a diagnosis of WM; nor is there a defined course of treatment or accurate prognosis. Thus, it is important that the patient obtain all available information, including seeking second opinions and additional consultations.

Resources

ORGANIZATIONS

Cure for Lymphoma Foundation. 215 Lexington Ave., New York, NY 10016. (212) 213-9595. (800)-CFL-6848. infocfl@cfl.org. <http://www.cfl.org/home.html>. An advocacy organization; education and support programs, research grants, information on clinical trials for Hodgkin's and non-Hodgkin's lymphomas.

International Waldenström's Macroglobulinemia Foundation. 2300 Bee Ridge Road, Sarasota, FL 34239-6226. (941) 927-IWMF. <http://www.iwmf.com>. Information, educational programs, support for patients and families, research support.

The Leukemia and Lymphoma Society. 600 Third Ave., New York, NY 10016. (800) 955-4572. (914) 949-5213. <http://www.leukemia-lymphoma.org>. Information, support, and guidance for patients and health care professionals.

The Lymphoma Research Foundation of America, Inc. 8800 Venice Boulevard, Suite 207, Los Angeles, CA 90034. (310) 204-7040). <http://www.lymphoma.org>. Research into treatments for lymphoma; educational and emotional support programs for patients and families.

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Warfarin

Definition

Wafarin is a vitamin K antagonist that belongs to the family of drugs called anticoagulants (''blood thinners,'' although it does not actually thin the blood). The brand name of warfarin in the U.S. is Coumadin.

Purpose

Wafarin is used to decrease the clotting ability of the blood and to help prevent harmful clots from forming in the blood vessels. It is also used for the long-term treatment of thromboembolic disease, a common side effect of cancer.

One of the most common hematological complications is disordered coagulation. Approximately 15% of all cancer patients are affected by thromboembolic disease, and it is the second leading cause of death for cancer patients. However, thromboembolic disease may represent only one of many complications in end-stage patients. Thromboembolic disease includes superficial and deep vein thrombosis, pulmonary embolism, thrombosis of venous access devices, arterial thrombosis, and embolism. The cancer itself or cancer treatments may induce coagulation. For example, **tamoxifen**, a drug prescribed to treat **breast cancer**, increases the chance of developing pulmonary embolism or deep vein thrombosis.

Cancer and its treatment can affect all three causes of thromboembolic disease including the alteration of blood flow, damage to the cells in blood vessels (endothelial cells), and enhancing procoagulants (precursors, such as fibrinogen or prothrombin, that mediate coagulation). Cancer can affect blood flow by mechanically affecting blood vessels close to a tumor. In addition, tumors cause angiogenesis, which may create complexes of blood vessels with a disordered appearance and flow (varying in magnitude and direction). **Chemotherapy** or tumors may directly damage endothelial cells. Procoagulants may be secreted into the blood stream by cancer cells or can be increased on the surface of cancer cells.

Description

Warfarin will not dissolve an existing blood clot, but it may prevent it from getting larger. When warfarin is taken orally, it is absorbed quickly from the gastrointestinal tract. It reaches a maximal plasma concentration in 90 minutes and stays in the bloodstream (i.e. its half-life) 36–42 hours. Warfarin circulates in the bloodstream attached to plasma proteins—in particular, a protein called albumin. The response or effects of a warfarin dose vary from person to person.

Whether anticoagulants like wafarin may also improve cancer survival rates independent of their effect on thromboembolism has been investigated. There is suggestive evidence that warfarin may actually enhance cancer survival rates. Animal studies show that warfarin and other agents such as **heparin**, fibrinolytics, and even antiplatelet agents inhibit tumor growth and **metastasis**.

Recommended dosage

A doctor may prescribe a dosage based on laboratory blood tests that determine a patient's clotting time. This blood test (called prothrombin time) is conducted usually weekly or monthly as suggested by a physician and should always be done at the same time of day. Based on the clotting time, the doctor determines the dose and/or whether the dose should be adjusted. Warfarin is normally prescribed to be taken once a day, and it should be taken at the same time every day.

Precautions

Following certain precautions when taking warfarin may reduce the risk of side effects and improve the effectiveness of the medication. The rate of blood clotting is affected by illness, diet, medication changes, and physical activities. If an individual has other medical problems, this may affect the use of warfarin. Of particular importance are bleeding ulcers, heavy menstrual periods, infections, high blood pressure, and liver or kidney problems. The doctor should be informed of any changes in these conditions so dose alterations can be made, if necessary. If a patient using warfarin is scheduled for surgery or dental work, the doctor or dentist should be informed that the patient is taking this medication. Warfarin should not be prescribed if an allergic reaction has occurred in the past, during pregnancy or while breastfeeding, or if pregnancy is planned. Anyone taking warfarin should exercise extra care not to cut him/herself

and not to sustain injuries that can result in bruising or bleeding.

In addition, patients taking warfarin should watch their intake of vitamin K, since too much vitamin K may alter the way in which warfarin works. The amount of foods high in vitamin K (such as broccoli, spinach, and turnip greens) eaten each week should be kept stable. Grapefruit juice should be avoided because it may intensify the effects of this medication. Alcohol should also be avoided while taking warfarin because it interferes with warfarin's effectiveness.

In order to determine a safe and effective dose, regular blood tests to check prothrombin time should be done while taking this medicine. Individuals taking warfarin frequently require dose adjustments.

Side effects

The most common complication of long-term warfarin therapy is bleeding. The intensity of anticoagulant therapy, age, kidney function, and unidentified diseases of the gastrointestinal and genitourinary tracts all directly influence the risk of bleeding. Patients taking warfarin should be aware of the signs and symptoms that may indicate a bleeding problem. These signs and symptoms include:

- bleeding from the gums or nose
- red or black bowel movements
- coughing up blood (hemoptysis)
- heavy bleeding from cuts or wounds that will not stop
- unusually heavy menstrual bleeding
- blood in the urine
- easy bruising or purple spots on the skin
- severe headache

The patient should inform his/her doctor immediately if any of these symptoms is present.

Other side effects that may occur with warfarin treatment include:

- mild stomach cramps
- upset stomach
- hair loss (alopecia)
- poor appetite (anorexia)
- cough or hoarseness
- fever or chills
- skin rash, hive, or itching
- painful or difficult urination

KEY TERMS

Angiogenesis—The formation of new blood vessels that occurs naturally under certain circumstances, for example, in the healing of a cut.

Anticoagulant—A medication that prevents the formation of new blood clots and keeps existing blood clots from growing larger.

Arterial thrombosis—A condition characterized by a blood clot in an artery.

Blood clot—A clump of blood that forms in or around a vessel as a result of coagulation. The formation of blood clots when the body has been cut is essential because without blood clots to stop the bleeding, a person would bleed to death from a relatively small wound.

Coagulation—The blood's natural tendency to clump and stick.

Embolism—An obstruction in a blood vessel due to a blood clot or other foreign matter that gets stuck while traveling through the bloodstream.

Embolus—A blood clot, gas bubble, piece of tumor tissue, or other foreign matter that moves through the bloodstream from its site of origin to obstruct a blood vessel.

Endothelial cells—The cells lining the inside of blood vessels.

Fibrinolytics—Agents that decompose fibrin, a protein produced in the clotting process.

Pulmonary embolism—A blockage of the pulmonary artery by foreign matter such as a blood clot.

Thromboembolic disease—A condition in which a blood vessel is obstructed by an embolus carried in the bloodstream from the site of formation.

Thrombosis—A condition in which a clot develops in a blood vessel.

Vein thrombosis—A condition characterized by a blood clot in a vein.

The occurrence of any of these side effects should also be reported to the doctor.

Interactions

Some medications should not be combined. The patient should check with the doctor monitoring the warfarin treatment before taking any new medication, including over-the-counter medication or medication prescribed by another doctor.

Among the medications and dietary supplements that may alter the way warfarin works are:

- other prescription medications
- nonprescription medications such as aspirin or nonsteroidal anti-inflammatory drugs (i.e. ibuprofen)
- cough or cold remedies
- herbal products and nutritional supplements
- products containing vitamin K

Studies have shown that Warfarin along with cranberry juice can be big trouble. The volume of the case studies included glasses of cranberry juice daily, not gallons. This drug-food interaction was shown to cause an increased risk of bleeding. This risk prompted the UK's Committee on Safety of Medicines and the Medicines and Healthcare Products Regulatory Agency to warn patients of warfarin to limit consumption of cranberry juice or avoid it altogether. According to Dr. Jacci Bainbrigde of the University of Colorado, Denver, "A cranberry juice/warfarin interaction is biologically plausible. Warfarin is metabolized chiefly by cytochrome P-450 in the liver, and the antioxidant flavonoids contained in the juice are known to inhibit the enzyme pathway." However, limited consumption is advised.

See also Low molecular weight heparin.

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Weight loss

Definition

Weight loss is a reduction in body mass characterized by a loss of adipose tissue (body fat) and skeletal muscle.

Description

Unintentional weight loss is the most common symptom of cancer and often a side effect of cancer treatments. A poor response to cancer treatments, reduced quality of life, and shorter survival time may result from substantial weight loss. The body may become weaker and less able to tolerate cancer therapies. As body weight decreases, body functionality declines and may lead to malnutrition, illness, infection, and perhaps death.

Most cancer patients in the United States expect to suffer weight loss during treatment for their disease; a study of 938 patients from 17 communities in upstate New York reported in 2004 that weight loss was the fourth most commonly expected side effect of cancer therapy, after fatigue, nausea, and sleep disturbances.

Severe malnutrition is typically defined in two ways: functionally (increased risk of morbidity and/or mortality) and by degree of weight loss (greater than 2% per week, 5% per month, 7.5% per 3 months, and 10% per 6 months). Without considering a specific time course, grading is as follows:

- Grade 0 = less than 5.0% weight loss
- Grade 1 = 5.0% to 9.9%
- Grade 2 = 10.0% to 19.9%
- Grade 3 = greater than 20.0%
- Grade 4 (life-threatening) is not specifically defined. Paying attention to weight loss at an early stage is necessary to prevent deterioration of weight, body composition, and performance status.

Causes

There are many reasons for weight loss in cancer patients, including appetite loss because of the effect of cancer treatments (**chemotherapy**, **radiation therapy**, or biological therapy) or psychological factors such as **depression**. Patients may suffer from **anorexia** and lose desire to eat, and thus consume less energy. When inadequate calories are consumed, it can lead to "wasting" of body stores (muscle and adipose tissue). Weight loss may be temporary or may continue at a life-threatening pace.

Weight loss may be also be a consequence of an increased requirement for calories (energy) due to infection, **fever**, or the effects of the tumor or cancer treatments. If infection or fever is present, it is necessary to consider that there is an increased caloric need of approximately 10% to 13% per degree above 98.6°F (37°C). Therefore, energy intake has to be increased to account for this rise in body temperature.

Weight loss may be a result of a common problem in cancer called cachexia. Approximately half of all cancer patients experience cachexia, a wasting syndrome that induces metabolic changes leading to a loss of muscle and fat. It has been proposed that cachexia may be due to the effects of the tumor, but this is debatable considering some patients with very large tumors do not experience cachexia, while others do even though tumors are less than 0.01% of body mass. Cachexia is most common in patients with pancreatic and gastric cancer. Approximately 83% to 87% of these patients experience weight loss. Cachexia is characterized by such symptoms as decreased appetite, **fatigue**, and poor performance sta-

tus. It can occur in individuals who consume enough food, but due to disease complications, cannot absorb enough nutrients (i.e. fat malabsorption). Although energy expenditure is sometimes increased, cachexia can occur even with normal energy expenditure. Cachexia is multifactorial in nature and associated with mechanical factors, psychological factors, changes in taste, and cytokines. It should be distinguished from anorexia, in which there is a loss of desire to eat, resulting in weight loss. Cachexia is a serious complication in cancer patients, thought to be responsible for as many as 20% of all deaths from cancer.

Special concerns

In order to allow normal tissue repair following aggressive cancer therapies, patients require adequate calories and macronutrients in the form of protein, carbohydrates, and fat. Inadequate consumption of food and/or poor nutrition may impair the ability of a patient to tolerate a specific therapy. If a low tolerance to therapy necessitates a decrease in dose, the therapy's effectiveness could be compromised. Wound healing may also be impaired with poor nutrition and inadequate energy intake.

Research has demonstrated that men often experience significantly more weight loss than women over the course of the disease and lose weight much faster. On average, survival time for men is shorter than for women. Significant predictors of patient survival are stage of disease, initial weight-loss rate, and gender.

Treatments

Nutritional problems related to side effects should be addressed to ensure adequate nutrition and prevent weight loss. In particular, cancer patients should maintain an adequate intake of calories and protein to prevent protein-calorie malnutrition. The patient's caloric requirements can be calculated by a dietitian or doctor since nutrient requirements vary considerably from patient to patient. Moreover, patient education about nutrition is vitally important; several recent studies have shown that almost half of all cancer patients in the United States receive no nutritional information from health care professionals, including the 18% who experience significant weight loss.

The following dietary tips may help patients to reduce weight loss:

- Eat more when feeling the hungriest.
- Eat foods that are enjoyed the most.
- Eat several small meals and snacks instead of three large meals. A regular meal schedule should be kept so meals are not missed.
- Have ready-to-eat snacks on hand such as cheese and crackers, granola bars, muffins, nuts and seeds, canned puddings, ice cream, yogurt, and hard boiled eggs.
- Eat high-calorie foods and high-protein foods.
- Take a small meal as to enjoy the satisfaction of finishing a meal. Have seconds if still hungry.
- Eat in a pleasant atmosphere with family and friends if desired.
- Make sure to consume at least eight to 10 glasses of water per day to maintain fluid balance.
- Consider commercial liquid meal replacements such as Ensure, Boost, Carnation, and Sustacal.

An appetite stimulant may be given in order to prevent further weight loss such as **megestrol acetate** or **dexamethasone**. In **clinical trials**, both these medications appear to have similar and effective appetite stimulating effects with megestrol acetate having a slightly better toxicity profile. **Fluoxymesterone** has shown inferior efficacy and an unfavorable toxicity profile.

As of 2004, researchers at the Medical College of Virginia are studying a group of compounds known as cannabinoids for the treatment of cachexia and vomiting associated with cancer treatment. The best-known natural cannabinoids are derived from marijuana.

Further research is needed in order to devise an effective treatment for the loss of muscle tissue in cachexia. As of 2004, there are no medications, nutritional supplements, or other treatments that are even moderately successful in reversing the wasting of muscle tissue in cachexia.

Alternative and complementary therapies

Depression may affect approximately 15%–25% of cancer patients, particularly if the prognosis for recovery is poor. If anorexia is due to depression, there are antidepressant choices available through a physician. Counseling may be also be sought through a psychologist or psychiatrist to cope with depression.

It is important to check with a dietitian or doctor before taking nutritional supplements or alternative therapies because they may interfere with cancer medications or treatments. St. John's Wort has been used as a herbal remedy for treatment of depression, but it and prescription antidepressants is a dangerous combination that may cause symptoms such as nausea, weakness, and may cause one to become incoherent.

See also Taste alteration.

KEY TERMS

Anorexia—A condition frequently observed in cancer patients characterized by a loss of appetite or desire to eat.

Cachexia—A condition in which the body weight "wastes" away, characterized by a constant loss of weight, muscle, and fat.

Cancer—A group of diseases in which abnormal cells divide without control. Cancer cells can invade nearby tissues and can spread through the bloodstream and lymphatic system to other parts of the body.

Chemotherapy—Chemotherapy kills cancer cells using drugs taken orally or by needle in a vein or muscle. It is referred to as a systemic treatment due to fact that it travels through the bloodstream and kills cancer cells outside the small intestine.

Enteral nutrition—Feedings administered through a nose tube (or surgically placed tubes) for patients with eating difficulties.

Parenteral nutrition—Feeding administered most often by an infusion into a vein. It can be used if the gut is not functioning properly or due to other reasons that prevent normal or enteral feeding.

Protein-calorie malnutrition—A lack of sufficient protein and calories to sustain the body's composition, resulting in weight loss and muscle wasting.

Radiation therapy—Also called radiotherapy; uses high-energy rays to kill cancer cells.

Wasting—When inadequate calories are consumed, it can lead to depletion of body mass. Wasting results in weight loss in tissues such as skeletal muscle and adipose tissue (fat).

Resources

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ORGANIZATIONS

American Institute for Cancer Research. 1759 R Street NW, Washington, D.C. 20009. (800) 843-8114 or (202) 328-7744. <http://www.aicr.org>, e-mail: support@aicr.org.

American Society for Clinical Nutrition. 9650 Rockville Pike, Bethesda, MD 20814-3998. (301) 634-7110. Fax: (301) 634-7350. <http://www.ascn.org>.

National Cancer Institute (NCI). Public Inquiries Office: Building 31, Room 10A31, 31 Center Dr., MSC 2580, Betheseda, MD 20892-2580 (301) 435-3848, (800) 4-CANCER, <http://cancer.gov/publications/>, <http://cancertrials.nci.nih.gov>, <http://cancernet.nci.nih.gov>.

National Center for Complementary and Alternative Medicine (NCCAM). 31 Center Dr., Room #5B-58, Bethesda, MD 20892-2182. (800) NIH-NCAM, Fax (301) 495-4957. <http://nccam.nih.gov>.

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Wilms' tumor

Definition

Wilms' tumor is a cancerous tumor of the kidney that usually occurs in young children. It is named for Max Wilms, a German surgeon (1867–1918) and is also known as a nephroblastoma.

Description

When an unborn baby is developing, the kidneys are formed from primitive cells. Over time, these cells

become more specialized. The cells mature and organize into the normal kidney structure. Sometimes, clumps of these cells remain in their original, primitive form. If these cells begin to multiply after birth, they may ultimately form a large mass of abnormal cells. This is known as a Wilms' tumor.

Wilms' tumor is a type of malignant tumor. This means that it is made up of cells that are significantly immature and abnormal. These cells are also capable of invading nearby structures within the kidney and traveling out of the kidney into other structures. Malignant cells can even travel through the body to invade other organ systems, most commonly the lungs and brain. These features of Wilms' tumor make it a type of cancer that, without treatment, would eventually cause death. However, advances in medicine during the last 20 years have made Wilms' tumor a very treatable form of cancer.

Wilms' tumor occurs almost exclusively in young children. The average patient is about three years old, although cases have also been reported in infants younger than six months and adults in their early twenties. Females are only slightly more likely than males to develop Wilms' tumors. In the United States, Wilms' tumor occurs in 8.3 individuals per million in white children under the age of 15 years. The rate is higher among African-Americans and lower among Asian-Americans. Wilms' tumors are found more commonly in patients with other types of congenital conditions. These conditions include:

- absence of the colored part (the iris) of the eye (aniridia)
- enlargement of one arm, one leg, or half of the face (hemihypertrophy)
- certain birth defects of the urinary system or genitals
- certain genetic syndromes (WAGR syndrome, Denys-Drash syndrome, and Beckwith-Wiedemann syndrome)

Causes and symptoms

The cause of Wilms' tumor is not completely understood. Because 15% of all patients with this type of tumor have other heritable defects, it seems clear that at least some cases of Wilms' tumor are due to an inherited alteration. A genetic defect known as WT1, the Wilms' tumor suppressor gene, has been identified in some patients on chromosome 11. It appears that the tendency to develop a Wilms' tumor can run in families. In fact, about 1.5% of all children with a Wilms' tumor have family members who have also had a Wilms' tumor. The genetic mechanisms associated with the disease are unusually complex; it is thought as of 2004 that the tumor develops because the defective WT1 gene fails to stop its growth. Other genes that have been linked to Wilms' tumor are located on chromosomes 16q, 7p15, and 17q12.

Some patients with Wilms' tumor experience abdominal pain, nausea and vomiting, high blood pressure, or blood in the urine. However, the parents of many children with this type of tumor are the first to notice a firm, rounded mass in their child's abdomen. This discovery is often made while bathing or dressing the child and frequently occurs before any other symptoms appear. Rarely, a Wilms' tumor is diagnosed after there has been bleeding into the tumor, resulting in sudden swelling of the abdomen and a low red blood cell count (**anemia**).

About 4–5% of Wilms' tumor cases involve both kidneys during the initial evaluation. The tumor appears on either side equally. When pathologists look at these tumor cells under the microscope, they see great diversity in the types of cells. Some types of cells are associated with a more favorable outcome in the patient than others. In about 15% of cases, physicians find some degree of cancer spread (**metastasis**). The most common sites in the body where metastasis occurs are the liver and lungs.

Researchers have found evidence that certain types of lesions occur before the development of the Wilms' tumor. These lesions usually appear in the form of stromal, tubule, or blastemal cells.

Diagnosis

Children with Wilms' tumor generally first present to physicians with a swollen abdomen or with an obvious abdominal mass. The physician may also find that the child has **fever**, bloody urine, or abdominal pain. The physician will order a variety of tests before imaging is performed. These tests mostly involve blood analysis in the form of a white blood cell count, complete blood count, platelet count, and serum calcium evaluation. Liver and kidney function testing will also be performed as well as a urinalysis.

Initial diagnosis of Wilms' tumor is made by looking at the tumor using various imaging techniques. Ultrasound and **computed tomography** scans (CT scans) are helpful in diagnosing Wilms' tumor. Intravenous pyelography, where a dye injected into a vein helps show the structures of the kidney, can also be used in diagnosing this type of tumor. Final diagnosis, however, depends on obtaining a tissue sample from the mass (**biopsy**), and examining it under a microscope in order

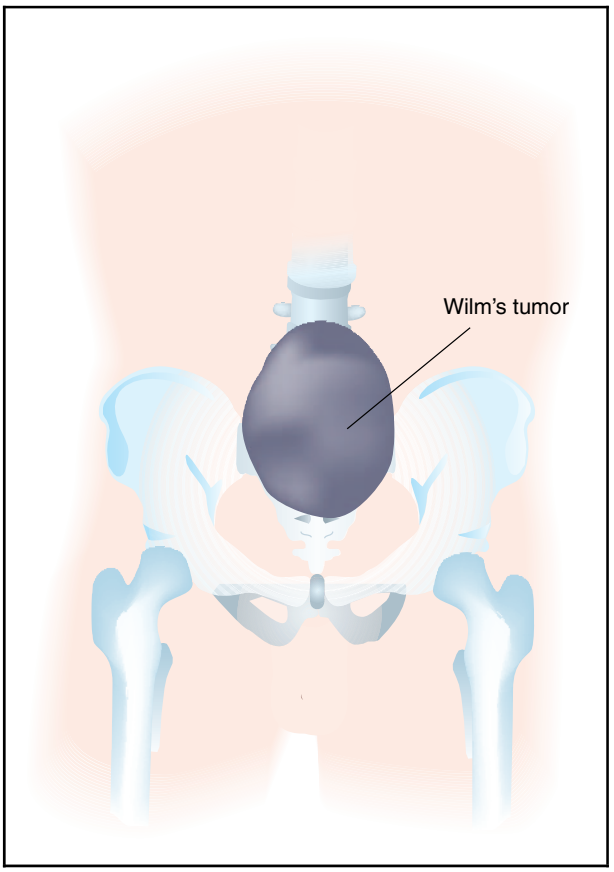
to verify that it has the characteristics of a Wilms' tumor. This biopsy is usually done during surgery to remove or decrease the size of the tumor. Other studies (chest x rays, CT scan of the lungs, bone marrow biopsy) may also be done in order to see if the tumor has spread to other locations.

Treatment

In the United States, treatment for Wilms' tumor almost always begins with surgery to remove or decrease the size of the kidney tumor. Except in patients who have tumors in both kidneys, this surgery usually will require complete removal of the affected kidney. During surgery, the surrounding lymph nodes, the area around the kidneys, and the entire abdomen will also be examined. While the tumor can spread to these surrounding areas, it is less likely to do so compared to other types of cancer. In cases where the tumor affects both kidneys, surgeons will try to preserve the kidney with the smaller tumor by removing only a portion of the kidney, if possible. Additional biopsies of these areas may be done to see if the cancer has spread. The next treatment steps depend on whether/where the cancer has spread. Samples of the tumor are also examined under a microscope to determine particular characteristics of the cells making up the tumor.

Information about the tumor cell type and the spread of the tumor is used to decide the best kind of treatment for a particular patient. Treatment is usually a combination of surgery, medications used to kill cancer cells (**chemotherapy**), and x rays or other high-energy rays used to kill cancer cells (**radiation therapy**). These therapies are called adjuvant therapies, and this type of combination therapy has been shown to substantially improve outcome in patients with Wilms' tumor. It has long been known that Wilms' tumors respond to radiation therapy. Likewise, some types of chemotherapy have been found to be effective in treating Wilms' tumor. These effective drugs include **dactinomycin**, **doxorubicin**, **vincristine**, and **cyclophosphamide**. In rare cases, **bone marrow transplantation** may be used.

The National Wilms' Tumor Study Group (NWTSG) has developed a staging system to describe Wilms' tumors. All of the stages assume that surgical removal of the tumor has occurred. Stage I involves "favorable" Wilms' tumor cells and is usually treated successfully with combination chemotherapy involving dactinomycin and vincristine and without abdominal radiation therapy. Stage II tumors involving a favorable histology (cell characteristics) are usually treated with the same therapy as Stage I. Stage III tumors with favorable histology are usually treated with a combination chemotherapy with doxorubicin, dactinomycin, and vincristine along with radiation therapy to the abdomen. Stage IV disease with a favorable histology is generally treated with combination chemotherapy with dactinomycin, doxorubicin, and vincristine. These patients usually receive abdominal radiation therapy and lung radiation therapy if the tumor has spread to the lungs.



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In the case of Stage II through IV tumors with unfavorable, or anaplastic, cells, then the previously mentioned combination chemotherapy is used along with the drug cyclophosphamide. These patients also receive lung radiation therapy if the tumor has spread to the lungs. Another type of tumor cell can be present in Stages I through IV. This cell type is called clear cell sarcoma of the kidney. If this type of cell is present, then patients receive combination therapy with vincristine, doxorubicin, and dactinomycin. All of these patients receive abdominal radiation therapy and

KEY TERMS

Biopsy—A procedure in which a small sample of tissue is removed, prepared, and examined with a microscope to determine the characteristics of the tissue's cells.

Blastemal—An immature material from which cells and tissues develop.

Cancer—A process where abnormal cells within the body begin to grow out of control, acquire the ability to invade nearby structures, and travel through the bloodstream in order to invade distant structures.

Congenital—Present at birth.

Malignant—Refers to cancer or cancer cells.

Sarcoma—A type of cancer that originates from connective tissue such as bone or muscle.

Stromal—A type of tissue that is associated with the support of an organ.

Tubule—Tissues and cells associated with the structures that connect the renal pelvis to the glomeruli.

lung radiation therapy if the tumor has spread to the lungs.

As of 2004, there are significant differences between the treatment protocols of the NWTSG and its European counterpart, the Société Internationale d'Oncologie Pédiatrique (SIOP). Whereas American practice favors surgery followed by chemotherapy, European oncologists use preoperative chemotherapy and stage the tumor at the time of surgery rather than at the point of initial imaging studies.

Prognosis

The prognosis for patients with Wilms' tumor is quite good, compared to the prognosis for most types of cancer. One German study reported the overall five-year survival rate to be 89.5%. The patients who have the best prognosis are usually those who have a small-sized tumor, a favorable cell type, are young (especially under two years old), and have an early stage of cancer that has not spread. Modern treatments have been especially effective in the treatment of this cancer. Patients with the favorable type of cell have a long-term survival rate of 93%, whereas those with anaplasia have a long-term survival rate of 43% and those with the sarcoma form have a survival rate of 36%.

Prevention

There are no known ways to prevent Wilms' tumor, although it is important that children with congenital conditions associated with Wilms' tumor be carefully monitored.

See also Intravenous urography.

Resources

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March of Dimes Birth Defects Foundation, National Office. 1275 Mamaroneck Ave., White Plains, NY 10605. <http://www.modimes.org>.

National Cancer Institute (National Institutes of Health). 9000 Rockville Pike, Bethesda, MD 20892. (800) 422-6237. <http://www.nci.nih.gov>.

National Wilms Tumor Study Group (NWTSG). Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, P. O. Box 19024, Seattle, WA 98109-1024. (800) 553-4878. Fax: (206) 667-6623. <http://www.nwtsg.org>.

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X

X rays

Definition

X rays are a type of radiation used in imaging and therapy that uses short wavelength energy beams capable of penetrating most substances except heavy metals.

Purpose

Diagnostic x rays are some of the most powerful medical imaging tools available. Other imaging techniques that do not use x rays include **magnetic resonance imaging** (MRI), ultrasonography, and radionucleotide imaging. Based on the symptoms presented by the patient, the physician can request specific x rays (such as chest x rays) that help diagnose many types of cancers, including **sarcomas**, lymphomas, and lung cancers. X rays allow the physician to visualize certain internal body conditions with little or no invasive procedures. Conditions may be visualized on photographic film, or for more complex and detailed information, **computed tomography** (CT scan), fluroscopy, or **angiography** might be used.

Precautions

Before consenting to any x-ray procedure, the patient should consider the impact of existing medical conditions or medications. Sensitivities to contrast dyes may produce allergic reactions. Pregnant women or those who suspect they might be pregnant should consult a physician prior to x-ray treatments to avoid injury to the fetus. Nursing mothers may be required to store enough milk to last for 48 hours following certain procedures. Patient age should always be taken into consideration when choosing the type and intensity of x ray. Patients should be aware that some prescribed cancer medications act as radiosensitizers and amplify the effect of x rays. Any patient with a suppressed immune system or diabetes may require special x-ray procedures.

Description

X-ray procedures are administered in a hospital or clinical setting. Most procedures may be conducted on an outpatient basis. The time required for the procedure may vary from a few minutes to more than an hour. There is little or no discomfort associated with diagnostic x rays. The general procedure for diagnostic x rays include:

- proper positioning and shielding of the patient
- administering contrast dyes, if necessary
- administering radiation
- review of the films by a technician to insure proper imaging
- Scheduling a time to review the films with the radiologist. However, if fluoroscopy or angiography is used, the procedure is dynamic (in motion), and the radiologist is present during the x ray administration.
- dismissal of the patient

Preparation

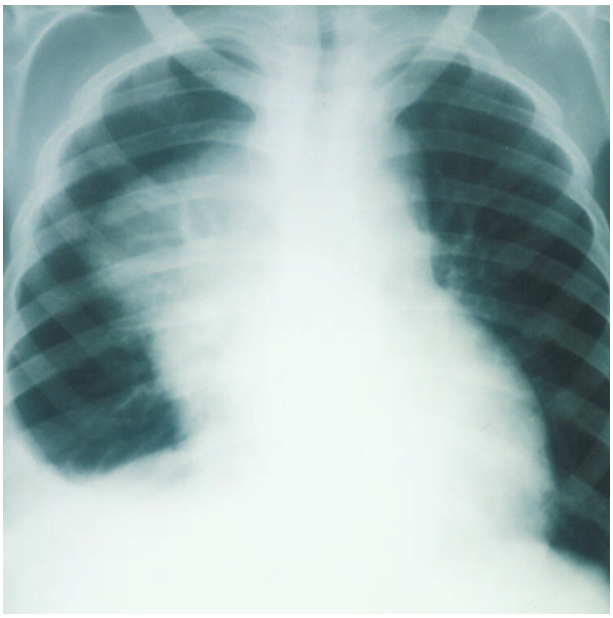
Diagnostic x rays require little preparation. The patient may be required to abstain from food and liquids for a certain period prior to the x ray. For some x rays, enemas may be necessary or a contrast agent may be administered immediately prior to or during the procedure.

Aftercare

For non-invasive diagnostic x-ray procedures, the patient is dismissed immediately after the films have been reviewed, and little or no aftercare is necessary.

Risks

A general rule for x rays suggests that the beneficial effects of x rays far exceed the risks involved. As a result of certified training and strict guideline compliance,



Chest x ray of patient with Hodgkin's disease. *(Custom Medical Stock Photo. Reproduced by permission.)*

risks from technical application are essentially nonexistent. However, for any x-ray procedure, radiation exposure is always a concern, and although uncommon, the risk of infection during invasive techniques can not be discounted.

Normal results

Diagnostic x rays provide detailed information that the physician can use to determine the best approach to correct or control a medical problem. Normal results would indicate no existing abnormalities.

Abnormal results

Abnormal results would indicate irregularities such as a tumor, an enlarged lymph node, or **pleural effusion**. Although highly unlikely, diagnostic x-ray films can be misread and the wrong diagnosis made.

See also Barium enema; Bone survey; CT-guided biopsy; Imaging studies; Intravenous urography; Lymphangiography; Nephrostomy; Pain management; Percutaneous transhepatic cholangiography; Radiation therapy.

KEY TERMS

Angiography—A radiographic technique in which an opaque contrast material is injected into a blood vessel for the purpose of identifying its anatomy on x ray.

Computed tomography (CT)—A special radiographic technique that uses a computer to convert multiple x-ray images into a two dimensional cross-sectional image.

Contrast dye—A radiopaque dye that allows enhancement of the anatomy demonstrable with conventional x ray.

Fluoroscopy—X-ray imaging of moving anatomic structures.

Gene therapy—The delivery of normal genes or genetically altered cells to the site of a tumor.

Interventional radiography—Diagnostic and therapeutic x-ray procedures that are invasive or surgical in nature but do not require the use of general anesthesia.

Pleural effusion—The accumulation of fluid in the pleural space, the region between the outer surface of each lung.

Radiologist—A physician specially trained in the use of x-rays for diagnostic and therapy purposes.

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QUESTIONS TO ASK THE DOCTOR

- What type of x-ray procedure is best to diagnosis my condition?
- Will the procedure or treatment hurt?
- How long will it take each time and how many treatments are required?
- What are my chances for a complete recovery?
- Are these procedures covered by insurance?

KEY TERMS

Oral cavity—The collective term for several structures in the mouth: the lips, teeth, gums, tongue, pharynx, and salivary glands.

Sialogogue—A medication given to increase the flow of saliva.

Xerostomia—The medical term for dry mouth.

Xerostomia

Description

Xerostomia, also known as dry mouth, is marked by a significant reduction in the secretion of saliva. Signs and symptoms of xerostomia include:

- dryness of the mouth
- cracked lips, cuts, or cracks at the corners of the mouth
- taste changes
- a burning sensation of the tongue
- changes in the surface of the tongue
- difficulty wearing dental appliances (like dentures)
- difficulty swallowing fluids accompanied by an increase in thirst Xerostomia makes the mouth less able to neutralize acid, clean the teeth and gums, and protect itself from infection. This can lead to the development of gum disease and cavities.

Saliva is necessary for carrying out the normal functions of the oral cavity, such as taste, speech, and swallowing. Saliva provides calcium and phosphate, minerals that protect the teeth against softening. It also contains substances inhibiting the production of bacteria that cause tooth decay. In addition, saliva buffers the acids produced when leftover food particles are broken down by bacteria.

Xerostomia causes the following mouth changes that can contribute to discomfort for the patient, and an increased risk for oral lesions:

- Saliva becomes thick and is less able to lubricate the mouth.
- Acids in the mouth cannot be neutralized, leading to mineral loss from the teeth.
- There is an increased risk for cavities because the mouth is less able to control bacteria.
- Plaque becomes thicker and heavier because of the patient's difficulty in maintaining good oral hygiene.
- The acid produced after eating or drinking sugary foods leads to further mineral loss from the teeth, causing even more tooth decay.

Causes

Xerostomia in cancer patients is primarily caused by the effects of **radiation therapy** on the salivary glands, usually the result of radiation to the head and neck area. These changes may occur rapidly and cannot normally be reversed, especially if the salivary glands themselves are irradiated. Within one week of starting radiation treatment, the production of saliva drops and continues to decrease as treatment continues. The severity of xerostomia is dependent upon the radiation dose and how many salivary glands are irradiated. Typically, the salivary glands inside the upper back cheeks (the parotid glands) are more affected than others. Salivary glands that are not irradiated may become more active as a way of compensating for the loss of saliva from the destroyed glands.

A number of medications can cause xerostomia, including many drugs used in the management of cancer or cancer treatment side effects. Some of these are: atropine, **amitriptyline**, **carbamazepine**, **diphenhydramine**, **gabapentin**, haloperidol, loperamide, **lorazepam**, **meperidine**, and **scopolamine**, among several others.

Xerostomia may develop in patients with HIV infection, as the virus often damages the salivary glands.

Lastly, xerostomia often accompanies the normal aging process; between 25 and 50% of people over the age of 65 complain of increasing dryness of mouth.

Treatments

A number of **clinical trials** are investigating drugs called radioprotectors, which are given at the time of

radiation therapy in an attempt to prevent xerostomia. If xerostomia has already developed, there are a number of measures that may help to both alleviate the symptoms of dry mouth and prevent cavities and gum disease. These measures include:

- cleaning the mouth well at least four times per day (after every meal and at bedtime)
- rinsing the mouth immediately after every meal
- using fluoride toothpaste to brush the teeth
- sipping water frequently
- rinsing the mouth with a salt and baking soda solution four to six times per day (1/2 tsp. salt, 1/2 tsp. baking soda, and 8 oz of water)
- avoiding foods and liquids containing large amounts of sugar
- avoiding mouthwashes containing alcohol
- using moisturizer on the lips
- using saliva substitutes to help relieve discomfort
- using a sialogogue such as **pilocarpine** (Salagen), which can stimulate saliva secretion from the remaining salivary glands
- applying a prescription-strength fluoride gel daily at bedtime to clean the teeth

Xerostomia usually cannot be reversed when the cause is the destruction of the salivary glands by radiation treatments. It may be reversible if related to a medication. All of the treatment measures serve to increase the level of comfort, decrease the chance for oral lesions, and reduce the occurrence of gum disease and cavities.

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Z

Zoledronate

Definition

Zoledronate, which is also known as zoledronic acid, is a treatment for **hypercalcemia** (high levels of calcium in the blood) caused by tumors. It is sold under the brand name Zometa. New laboratory evidence suggests that, in addition, zoledronate may have direct anticancer effects.

Purpose

Tumor-induced hypercalcemia is also known as hypercalcemia of malignancy. Tumor-induced hypercalcemia may be caused by a tumor spreading to and causing breakdown of bone, or by chemicals released from some tumors. The result is high levels of calcium in the blood. High levels of calcium may cause changes in mental status, constipation, and kidney damage.

Zoledronate was approved by the Food and Drug Administration (FDA) in 2002 as a treatment for multiple myeloma and bone metastases. Bone metastases may develop if cells from breast, lung, or other cancers are transplanted to bone by the disease process. Bone **metastasis** may cause pain, compression of the nerves of the spine, and bone fractures.

Other drugs in the same class as zoledronate are used to prevent pain or fractures in people with bone metastases. Zoledronate appears to be effective for this use as well, particularly in men being treated for prostate cancer. In addition, these drugs (the class of **bisphosphonates**) are being studied to see if they prevent the development of bone metastases in the first place.

Description

Zoledronate is one of a group of medicines known as bisphosphonates. Bisphosphonates prevent bone destruction by inhibiting the action of osteoclasts, cells that break down bone. As of 2004 zoledronate is one of the most potent bisphosphonates approved for use in the United States.

KEY TERMS

Bisphosphonates—A class of drugs that inhibit the action of osteoclasts—the cells that dissolve or break down bone.

Bone metastases—The spread of tumor cells from the primary site of origin to bone. Bone metastases from breast cancer, for example, represent breast cancer cells that have invaded bone. They are not the same as bone cancer cells that originate in bone.

Hypercalcemia of malignancy—Also called tumor-induced hypercalcemia; high levels of calcium in the blood from the dissolving of bone, either directly by cancer cells or indirectly by chemicals released from cancer cells.

Recommended dosage

As of 2002 the recommended dosage of zoledronate is 4 mg, given intravenously over a 15-minute period. This short infusion period gives zoledronate an advantage over other drugs in the bisphosphonate class; one study done in Australia found that patients preferred zoledronate to other intravenous bisphosphonates for this reason. The frequency of administration of zoledronate for hypercalcemia depends on the patient's calcium blood level.

Side effects

The most common side effects due to zoledronate that have been reported to date are **fever**, low blood concentration of phosphate, and low blood calcium (not low enough to cause symptoms). Overall, the drug appears to be well tolerated and safe for long-term use in cancer patients.

Resources

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ORGANIZATIONS

American Society of Health-System Pharmacists (ASHP). 7272 Wisconsin Avenue, Bethesda, MD 20814. (301) 657-3000. <www.ashp.org>.

United States Food and Drug Administration (FDA). 5600 Fishers Lane, Rockville, MD 20857-0001. (888) INFO-FDA. <www.fda.gov>.

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Zollinger-Ellison syndrome

Definition

In Zollinger-Ellison syndrome (ZES), a tumor (a gastrinoma) secretes the hormone gastrin, which stimulates the secretion of gastric acid. This leads to the development of ulcers in the stomach and duodenum (the first part of the small intestine).

Description

In normal individuals, the stomach secretes the hormone gastrin after food enters the stomach. Gastrin is carried by the bloodstream to other parts of stomach. The main effect of gastrin is to stimulate the parietal cells of the stomach. Parietal cells are stomach cells that secrete gastric acid to aid in digestion. This acid plays a vital role in the digestion of food. This process is highly regulated so that the stomach produces gastrin in significant amounts only when necessary, as when there is food in the stomach.

The underlying entity of ZES is a tumor called a gastrinoma which secretes gastrin inappropriately. Marked overproduction of gastrin leads to hypersecretion of gastric acid by the parietal cells. The end result is severe ulcers of the stomach and duodenum that are more difficult to treat than common ulcers.

Gastrinomas are generally small tumors located in the pancreas or duodenum. They often occur in multiples in the same patient. More than half of all gastrinomas are malignant, with the potential to spread to nearby lymph nodes and also spread to the liver and other organs by way of **metastasis**. The malignant potential of gastrinoma is ultimately more life-threatening than the associated ulcers.

The ulcers in ZES are frequently located further down the gastrointestinal tract than common ulcers, and they may be multiple.

About 25% of patients with ZES also demonstrate other tumors of the endocrine system in a syndrome called Multiple Endocrine Neoplasia syndrome.

Demographics

ZES occurs slightly more frequently in males than females. The average age of onset is between 30 and 50 years of age. It is difficult to determine the prevalence of ZES, but it is not a common syndrome.

Causes and symptoms

The symptoms of ZES are chiefly related to the ulcer disease. The main symptom is abdominal pain, present in the vast majority of patients. Ulcers can also cause nausea, vomiting, and heartburn. Compared with patients with common ulcers, patients with ZES generally have more severe and persistent symptoms that are more difficult to control. In some cases, the ulcers can bleed or actually perforate completely through the walls of the stomach or duodenum.

Many patients also suffer **diarrhea** in addition to ulcer pain. In fact, diarrhea is the only symptom in a small fraction of patients, and the diarrhea may precede the development of ulcers in the stomach and duodenum.

Diagnosis

A number of clinical circumstances suggest that a patient's ulcer disease may be due to ZES:

- ulcer disease resistant to conventional medical treatment
- recurrent ulcers after surgery intended to cure the ulcer disease
- ulcer disease in the absence of the usual risk factors for ulcers
- ulcers located in abnormal locations in the gastrointestinal tract
- multiple ulcers
- ulcers accompanied by diarrhea
- strong family history of ulcer disease

Diagnosis of ZES must be confirmed by observing abnormally high levels of gastrin in the blood. This is the hallmark of the disease. But it must be mentioned that the gastrinoma of ZES is not the only cause of hypersecretion of gastrin. ZES is distinguished from these other conditions by the presence of appropriate symptoms and high levels of gastrin and gastric acid. In cases where the diagnosis is not clear, several provocative tests can help determine if the patient has ZES. In the intravenous secretin injection test, a standard dose of the hormone secretin is injected intravenously. If the blood levels of gastrin respond by increasing a certain amount, the diagnosis is ZES. Similarly, in the intravenous calcium infusion test, a dose of calcium is injected and gastrin levels are measured. A substantial increase in the gastrin level points to ZES. A newer test measures the response in gastrin level to the ingestion of a standard meal. For example, the standard meal might be one slice of bread, one boiled egg, 200 mL of milk, and 50 gm of cheese.

Treatment team

The surgeon and gastroenterologists are the chief members of the treatment team. Radiologists play a vital role in the localization of the gastrinoma before surgery. Oncologists may be involved after surgery or if surgery is not indicated.

Clinical staging, treatments, and prognosis

The goal of treatment for ZES is the elimination of excess gastrin production, acid hypersecretion, ulcer disease, and malignant potential. This is achieved only by complete surgical removal of all gastrinomas. An attempt at surgical cure is offered to most patients, with the exception of those who already have widespread metastasis to the liver or who are too ill to undergo surgery. It is important to locate the gastrinoma(s) and any possible areas of metastasis before surgery. This can be accomplished with tests such as **computed tomography** (CT), ultrasound, **magnetic resonance imaging** (MRI), **angiography**, scintigraphy, and endoscopy. But as gastrinomas may be small, multiple, and hidden in atypical positions, finding the exact locations of all cancerous tissue can be challenging and sometimes impossible. In that case, surgeons will still proceed and attempt to find the tumor(s) at the time of operation. All identified gastrinoma should be removed if possible, including involved lymph nodes. Metastatic lesions in the liver can sometimes be safely removed, but only when they are isolated to one part of the liver.

Chemotherapy is sometimes able to reduce tumor size, which may relieve some symptoms due to local invasion or massive growth of the tumor. But it has not been shown to consistently prolong survival.

KEY TERMS

Angiography—Radiographic examination of blood vessels after injection with a special dye

Computed tomography—A radiology test by which images of cross-sectional planes of the body are obtained

Duodenum—The first portion of the small intestine in continuity with the stomach

Endoscopy—Examination of the interior of a hollow part of the body by means of a special, lighted instrument

Gastric—Of or relating to the stomach

Gastrin—Hormone normally secreted by the stomach that stimulates secretion of gastric acid

Gastrinoma—Tumor that secretes the hormone gastrin

Magnetic resonance imaging—A radiology test that reconstructs images of the body based on magnetic fields

Malignant—In reference to cancer, having the ability to invade local tissues and spread to distant tissues by metastasis

Metastasis—The spread of tumor cells from one part of the body to another

Parietal cells—Stomach cells that secrete gastric acid to aid in digestion

Scintigraphy—A radiology test that involves injection and detection of radioactive substances to create images of body parts

Ultrasound—A radiology test utilizing high frequency sound waves

Medical therapy plays a vital role in the treatment of ZES. A group of drugs known as proton pump inhibitors, which includes omeprazole (a drug used to treat common ulcers), is effective in decreasing acid secretion and promoting ulcer healing in patients with ZES. Omeprazole acts by blocking the last biochemical step in acid production. Omeprazole should be prescribed immediately after diagnosis. If surgery is not attempted, or ultimately unsuccessful, omeprazole is also useful for long-term treatment. For reasons that are not fully known, sometimes patients still require omeprazole after successful surgery. Another drug called octreotide is also effective in reducing acid secretion.

The prognosis for ZES depends primarily on whether or not the gastrinoma can be completely removed. If the cancer has spread diffusely to the liver, surgical cure is nearly impossible. The gastrinoma tissue is completely removed in about 40% of patients, resulting in reduced acid secretion and resolution of ulcer disease or diarrhea. These patients should expect a normal life expectancy, although they should undergo regular testing thereafter and may also require long-term omeprazole treatment. The prognosis is poor for patients in whom all the gastrinoma cannot be removed.

Clinical trials

In 2001, five **clinical trials** were recruiting patients with Zollinger-Ellison syndrome. These trials were studying various aspects of treatment for the syndrome, including the use of Omeprazole, interferon therapy, and combination chemotherapy. For further information about ongoing clinical trials, patients may consult the National Institutes of Health clinical trials site listed below.

See also Multiple endocrine neoplasia syndromes.

Resources

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Zolpidem

Definition

Zolpidem is a medicine that helps a person get to sleep and stay asleep. The brand name of zolpidem in the U.S. is Ambien.

Purpose

Zolpidem is a sleep medication. It is intended for the short-term treatment of insomnia. Zolpidem may be particularly useful for people who have trouble falling asleep.

Description

Sleep medications are called sedatives or hypnotics. Zolpidem affects brain chemicals, resulting in sleep. It is somewhat similar in its actions on sleep to the group of drugs known as benzodiazepines. Zolpidem is only intended for short term use (seven–10 days). Although there is some information published about effectiveness with longer use, some side effects may increase with longer use.

Recommended dosage

The usual dose is 10 mg before bedtime in adults and 5 mg before bedtime in the elderly and in people with liver disease. The onset of effect occurs within about 30 minutes and the effects on sleep last for 6–8 hours.

Precautions

It is suggested that zolpidem not be discontinued abruptly after regular use (that is daily use for even as short a time as one week). Instead, the drug should be gradually tapered. The tapering is recommended to avoid the possibility of a withdrawal syndrome as well as to avoid the possibility of a rebound worsening of insomnia.

Side effects

The most common side effects of zolpidem include drowsiness, dizziness, and headache. Drowsiness, of course, is desirable when it occurs at bedtime. Daytime drowsiness that is left over from the night before would be considered a side effect. Other side effects include **diarrhea**, nausea and vomiting, and muscle aches. Rarely, amnesia, confusion, falls, and tremor are seen. Falls probably result from the drowsiness or dizziness. There was also a reported study of a patient sleepwalking when taking Zolpidemalong with valproic acid. It is possible that the interactions between the two might have resulted in sleepwalking.

Interactions

Increased effects of zolpidem (eg. more drowsiness, confusion) may be seen with **alcohol consumption** and with other drugs known to cause drowsiness.

Bob Kirsch

APPENDIX I: NCI-DESIGNATED COMPREHENSIVE CANCER CENTERS

Comprehensive Cancer Centers have been designated as such by the National Cancer Institute. They are required to have basic laboratory research in several fields; to be able to transfer research findings into clinical practice; to conduct clinical studies and trials; to research cancer prevention and control; to offer information about cancer to patients, the public, and health care professionals; and to provide community service related to cancer control.

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Birmingham, AL 35294-3300
Tel: (205) 934-5077
Fax: (205) 975-7428
<http://www3.ccc.uab.edu/>

Arizona

Arizona Cancer Center
1501 North Campbell Avenue
Tucson, AZ 85724
Tel: (520) 626-7925
Fax: (520) 626-2284
<http://www.azcc.arizona.edu/Default6.htm>

California

The Burnham Institute Cancer Center
10901 North Torrey Pines Road
La Jolla, California 92037
Tel: (858) 646-3100
Fax: (858) 713-6274
<http://www.burnhaminstitute.org>

Chao Family Comprehensive Cancer Center
University of California at Irvine
101 The City Drive
Building 23, Rt. 81, Room 406
Orange, CA 92868
Tel: (714) 456-6310
Fax: (714) 456-2240
<http://www.ucihs.uci.edu/cancer/>

City of Hope National Medical Center & Beckman Research Institute
1500 E. Duarte Rd.
Duarte, CA 91010-3000
Tel: (626) 256-HOPE (4673)
Fax: (626) 930-5394
<http://www.cityofhope.org>

Jonsson Comprehensive Cancer Center
University of California Los Angeles
Factor Building, Room 8-684
10833 Le Conte Avenue
Los Angeles, CA 90095-1781
Tel: (310) 825-5268
Fax: (310) 206-5553
<http://www.cancer.mednet.ucla.edu/>

Rebecca and John Moores UCSD Comprehensive Cancer Center
University of California at San Diego
9500 Gilman Drive
La Jolla, CA 92093-0658
Tel: (858) 822-1222
Fax: (858) 822-1207
<http://cancer.ucsd.edu>

Salk Institute Cancer Center
10010 North Torrey Pines Road
La Jolla, CA 92037
Tel: (858) 453-4100
Fax: (858) 457-4765
<http://www.salk.edu/>

UC Davis Cancer Center
University of California, Davis
4501 X Street, Suite 3003
Sacramento, CA 95817
Tel: (916) 734-5800
Fax: (916) 451-4464
<http://www.ucdmc.ucdavis.edu/cancer/>

UCSF Comprehensive Cancer Center and Cancer Research Institute
University of California San Francisco
2340 Sutter Street, Box 0128
San Francisco, CA 94115-0128
Tel: (415) 502-1710
Fax: (415) 502-1712
<http://cc.ucsf.edu/>

USC/Norris Comprehensive Cancer Center
University of Southern California
1441 Eastlake Avenue,
NOR 8302L
Los Angeles, CA 90089-9181
Tel: (323) 865-0816
Fax: (323) 865-0102
<http://ccnt.hsc.usc.edu/>

Colorado

University of Colorado Cancer Center
University of Colorado Health Science Center
4200 East Ninth Avenue, Box B188
Denver, CO 80262
Tel: (303) 724-3155
Fax: (303) 315-3304
<http://www.uccc.info/>

Connecticut

Yale Cancer Center
Yale University School of Medicine
333 Cedar Street, Box 208028
New Haven, CT 06520-8028
Tel: (203) 785-4371
Fax: (203) 785-4116
<http://www.info.med.yale.edu/ycc/>

District of Columbia

Lombardi Cancer Research Center
Georgetown University Medical Center
3800 Reservoir Road, NW
Washington, DC 20007
Tel: (202) 687-2110
Fax: (202) 687-6402
<http://lombardi.georgetown.edu/>

Florida

H. Lee Moffitt Cancer Center and Research Institute
University of South Florida
12902 Magnolia Drive, MCC-CEO
Tampa, FL 33612-9497
Tel: (813) 615-4261
Fax: (813) 615-4258
<http://www.moffitt.usf.edu/>

Hawaii

Cancer Research Center of Hawaii
University of Hawaii at Manoa
1236 Lauhala Street
Honolulu, HI 96813
Tel: (808) 586-3013
Fax: (808) 586-3052
<http://www.crch.org>

Illinois

Robert H. Lurie Comprehensive Cancer Center
Northwestern University
303 East Chicago Avenue
Olson Pavillion 8250
Chicago, IL 60611
Tel: (312) 908-5250
Fax: (312) 908-1372
<http://cancer.northwestern.edu/home/index.cfm>

University of Chicago Cancer Research Center
5841 South Maryland Avenue, MC 2115
Chicago, IL 60637-1470
Tel: (773) 702-9306
Fax: (773) 702-3002
<http://www-uccrc.uchicago.edu/>

Indiana

Indiana University Cancer Center
Indiana Cancer Pavilion
535 Barnhill Drive, Room 455
Indianapolis, IN 46202-5289
Tel: (317) 278-0070
Fax: (317) 278-0074
<http://iucc.iu.edu/>

Purdue University Cancer Center
Hansen Life Sciences Research Building
South University Street
West Lafayette, Indiana 47907-1524
Tel: (765) 494-9129
Fax: (765) 494-9193
<http://www.cancer.purdue.edu/>

Iowa

Holden Comprehensive Cancer Center
University of Iowa
5970 "Z" JPP
200 Hawkins Drive
Iowa City, IA 52242
Tel: (319) 353-8620
Fax: (319) 353-8988
<http://www.uihealthcare.com/depts/cancercenter/>

Maine

The Jackson Laboratory Cancer Center
600 Main Street
Bar Harbor, ME 04609-0800
Tel: (207) 288-6041
Fax: (207) 288-6044
<http://www.jax.org>

Maryland

The Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins
401 North Broadway
The Weinberg Building, Suite 1100
Baltimore, MD 21231
Tel: (410) 955-8822
Fax: (410) 614-6787
<http://www.hopkinskimmelcancercenter.org/index.cfm>

Massachusetts

Center for Cancer Research
Massachusetts Institute of Technology
77 Massachusetts Avenue, Room E17-110
Cambridge, MA 02139-4307
Tel: (617) 253-8511
Fax: (617) 253-0262
<http://web.mit.edu/ccr/index.html>

Dana-Farber/Harvard Cancer Center
Dana-Farber Cancer Institute
44 Binney Street, Room 1628
Boston, MA 02115
Tel: (617) 632-4266
Fax: (617) 632-2161
<http://www.dfhcc.harvard.edu/pub_index.shtml?bhcp=1>

Michigan

Comprehensive Cancer Center
University of Michigan
6303 CGC/0942
1500 Easdt Medical Center Drive
Ann Arbor, MI 48109-0942
Tel: (734) 936-1831
Fax: (734) 615-3947
<http://www.cancer.med.umich.edu/>

The Meyer L. Prentis Comprehensive Cancer Center of Metropolitan Detroit
Barbara Ann Karmanos Cancer Institute
Wayne State University
4100 John R
Detroit, MI 48201
Tel: (313) 993-7770
Fax: (313) 993-7165
<http://www.karmanos.org>

Minnesota

Mayo Clinic Cancer Center
Mayo Clinic Rochester
200 First Street, S.W.
Rochester, MN 55905
Tel: (507) 284-3753
Fax: (507) 284-9349
<http://mayoresearch.mayo.edu/mayo/research/cancercenter/>

University of Minnesota Cancer Center
MMC 806, 420 Delaware Street, S.E.
Minneapolis, MN 55455
Tel: (612) 624-8484

Fax: (612) 626-3069
<http://www.cancer.umn.edu/>

Missouri

Siteman Cancer Center
Washington University School of Medicine
660 South Euclid Avenue, Campus Box 8109
St. Louis, MO 63110
Tel: (314) 362-8020
Fax: (314) 454-1898
<http://www.siteman.wustl.edu>

Nebraska

Eppley Cancer Center
University of Nebraksa Medical Center
600 South 42nd Street
Omaha, NE 68198-6805
Tel: (402) 559-4238
Fax: (402) 559-4652
<http://www.unmc.edu/cancercenter/>

New Hampshire

Norris-Cotton Cancer Center
Dartmouth-Hitchcock Medical Center
One Medical Center Drive, Hinman Box 7920
Lebanon, NH 03756-0001
Tel: (603) 653-9000
Fax: (603) 653-9003
<http://www.cancer.dartmouth.edu/index.shtml>

New Jersey

The Cancer Institute of New Jersey
Robert Wood Johnson University Hospital and Medical School
195 Little Albany Street, Room 2002B
New Burnswick, NJ 08901
Tel: (732) 235-8064
Fax: (732) 235-8094
<http://www.cinj.org>

New York

Cancer Research Center
Albert Einstein College of Medicine
Chanin Building, Room 209
1300 Morris Park Avenue
Bronx, NY 10461
Tel: (718) 430-2302
Fax: (718) 430-8550
<http://www.aecom.yu.edu/cancer/new/default.htm>

Cold Spring Harbor Laboratory Cancer Center
P.O. Box 100
Cold Spring Harbor, NY 11724
Tel: (516) 367-8383
Fax: (516) 367-8879
<http://www.cshl.org>

Herbert Irving Comprehensive Cancer Center
College of Physicians and Surgeons
Columbia University
161 Fort Washington Avenue
11th Floor, Room 1153
New York, NY 10032
Tel: (212) 305-5201
Fax: (212) 305-6813
<http://www.ccc.columbia.edu/>

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021
Tel: (212) 639-2000 or (800) 525-2225
Fax: (212) 717-3299
<http://www.mskcc.org/mskcc/html/44.cfm>

NYU Cancer Institute
New York University Medical Center
550 First Avenue
New York, NY 10016
Tel: (212) 263-8950
Fax: (212) 263-8210
<http://www.med.nyu.edu/nyuci/>

Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263-0001
Tel: (716) 845-5772
Fax: (716) 845-8261
<http://www.roswellpark.org/>

North Carolina

Comprehensive Cancer Center
Wake Forest University
Medical Center Blvd.
Winston-Salem, NC 27157-1082
Tel: (336) 716-7971
Fax: (336) 716-0293
<http://www1.wfubmc.edu/cancer>

Duke Comprehensive Cancer Center
Duke University Medical Center
Box 3843
Durham, NC 27710
Tel: (919) 684-5613
Fax: (919) 684-5653
<http://cancer.duke.edu/>

UNC Lineberger Comprehensive Cancer Center
University of North Carolina Chapel Hill
School of Medicine, CB-7295
102 West Drive
Chapel Hill, NC 27599-7295
Tel: (919) 966-3036
Fax: (919) 966-3015
<http://cancer.med.unc.edu/>

Ohio

Case Comprehensive Cancer Center
Case Western Reserve University
11100 Euclid Avenue, Wearn 151
Cleveland, OH 44106-5065
Tel: (216) 844-8562
Fax: (216) 844-4975
<http://cancer.case.edu>

Arthur G. James Cancer Hospital and
Richard J. Solove Research Institute
Ohio State University
A458 Staring Lobing Hall
320 West 10th Avenue
Columbus, OH 43210
Tel: (614) 293-7521
Fax: (614) 293-7522
<http://www.jamesline.com>

Oregon

OHSU Cancer Institute
Oregon Health & Science University
3181 S.W. Sam Jackson Park Road, CR 145
Portland, OR 97201-3098
Tel: (503) 494-1617
Fax: (503) 494-7086
<http://www.ohsucancer.org>

Pennsylvania

Abramson Cancer Center
University of Pennsylvania
16th Floor Penn Tower
3400 Spruce Street
Philadelphia, PA 19104-4283
Tel: (215) 662-6065

Fax: (215) 349-5325
<http://www.penncancer.org/>

Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, PA 19111
Tel: (215) 728-2781
Fax: (215) 728-2571
<http://www.fccc.edu/>

Kimmel Cancer Center
Thomas Jefferson University
233 South 10th Street
BLSB, Room 1050
Philadelphia, PA 19107-5799
Tel: (215) 503-4645
Fax: (215) 923-3528
<http://www.kcc.tju.edu>

University of Pittsburgh Cancer Institute
UPMC Cancer Pavilion
5150 Centre Avenue, Suite 500
Pittsburgh, PA 15232
Tel: (412) 623-3205
Fax: (412) 623-3210
<http://www.upci.upmc.edu/index>

The Wistar Institute Cancer Center
3601 Spruce Street
Philadelphia, PA 19104-4268
Tel: (215) 898-3926
Fax: (215) 573-2097
<http://www.wistar.upenn.edu/>

Tennessee

St. Jude Children's Research Hospital
332 North Lauderdale
P.O.Box 318
Memphis, TN 38105-2794
Tel: (901) 495-3982
Fax: (901) 495-3966
<http://www.stjude.org>

Vanderbilt-Ingraham Cancer Center
Vanderbilt University
691 Preston Research Building
Nashville, TN 37232-6838
Tel: (615) 936-1782
Fax: (615) 936-1790
<http://www.vicc.org/>

Texas

M.D. Anderson Cancer Center
University of Texas
1515 Holcombe Boulevard, Box 91
Houston, TX 77030
Tel: (713) 792-2121
Fax: (713) 799-2210
<http://www.mdanderson.org/>

San Antonio Cancer Institute
University of Texas Health Science Center at San Antonio
Department of Hematology
7703 Floyd Curl Drive
San Antonio, TX 78229-3900
Tel: (210) 567-4848
Fax: (210) 567-1956
<http://saci.uthscsa.edu/>

Utah

Huntsman Cancer Institute
University of Utah
2000 Circle of Hope
Salt Lake City, UT 84112-5550
Tel: (801) 585-3401
Fax: (801) 585-6345
<http://www.hci.utah.edu/>

Vermont

Vermont Cancer Center
University of Vermont
149 Beaumont Avenue, HRSF326
Burlington, VT 05405
Tel: (802) 656-4414
Fax: (802) 656-8788
<http://www.vermontcancer.org>

Virginia

Cancer Center
University of Virginia, Health Sciences Center
Jefferson Park Avenue, Room 617E
Charlottesville, VA 22908
Tel: (434) 243-9926
Fax: (434) 982-0918
<http://www.healthsystem.virginia.edu/internet/cancer/>

Massey Cancer Center
Virginia Commonwealth University
P.O. Box 980037
Richmond, VA 23298-0037
Tel: (804) 828-0450
Fax: (804) 828-8453
<http://www.vcu.edu/mcc>

Washington

Fred Hutchinson Cancer Research Center
P.O. Box 19024, D1-060
Seattle, WA 98109-1024
Tel: (206) 667-4305
Fax: (206) 667-5268
<http://www.fhcrc.org/>

Wisconsin

Comprehensive Cancer Center
University of Wisconsin
600 Highland Avenue, Room K4/610 Madison,
WI 53792-0001
Tel: (608) 263-8610

APPENDIX II: NATIONAL SUPPORT GROUPS

African American Breast Cancer Alliance (AABCA)
P.O. Box 8981
Minneapolis, MN 55408-0981
Tel: (612) 825-3675
E-mail: aabacainc@yahoo.com
Web: <http://www.geocities.com/aabcainc/>
Breast cancer support for patients, families, and communities.

ALCASE - Alliance for Lung Cancer Advocacy, Support, and Education
P.O. Box 849
500 West Eighth Street, Suite 240
Vancouver, WA 98660
Tel: (800) 298-2436
Fax: (360) 735-1305
E-mail: info@alcase.org
Web: <http://www.alcase.org>
Education, regional support group referrals, and Phone Buddies program.

American Brain Tumor Association (ABTA)
2720 River Rd, Suite 146
Des Plaines, IL 60018
Tel: (800) 886-ABTA
Fax: (847) 827-9918
E-mail: info@abta.org
Web: <http://hope.abta.org/site/PageServer>
Brain tumor information, support, and resources.

American Cancer Society (ACS)
2200 Century Parkway, Suite 950
Atlanta, GA, 30345
Tel: (800) ACS-2345
Fax: (404) 315-9348
Web: <http://www.cancer.org>

American Foundation for Urologic Disease (AFUD)
1000 Corporate Boulevard, Suite 410
Linthicum, MD 21090
Tel: (800) 828-7866
Fax: (410) 689-3998
E-mail: admin@afud.org
Web: <http://www.afud.org>

American Liver Foundation
75 Maiden Lane, Suite 603
New York, NY 10038
Tel: (800) GO-LIVER
Web: <http://www.liverfoundation.org>

American Lung Association (ALA)
61 Broadway, 6th Floor
New York, NY 10006
Tel: (800) LUNGUSA
Fax: (212) 315-8872
E-mail: info@lungusa.org
Web: <http://www.lungusa.org>
Promotes research, education, and advocacy for prevention of lung disease.

Association of Cancer Online Resources (ACOR)
<http://www.acor.org>
Links.

Association for Research of Childhood Cancer (AROCC)
P.O. Box 251
Buffalo, NY 14225-0251
Tel: (716) 681-4433
E-mail: odonnell@msn.org
Web: <http://www.arocc.org>
Provides support to parents of children with cancer.

Brain Tumor Foundation for Children
1835 Savoy Drive, Suite 316
Atlanta, GA 30341
Tel: (770) 458-5554
Fax: (404)458-5467
E-mail: btfc@bellsouth.net
Web: <http://www.btfcgainc.org/index.asp>
Brain tumor information, support, and resources for families of children with brain tumors.

The Brain Tumor Society
124 Watertown St., Suite 3-H
Watertown, MA 02472
Tel: (800) 770-8287
Web: <http://www.tbts.org>

Cancer Care, Inc.
275 Seventh Ave.
New York, NY 10001-6708
Tel: (800) 813-4673
Fax: (212) 712-8495
E-Mail: info@cancercare.org
Web: <http://www.cancercare.org>
Assists patients and families with the emotional, psychological, and financial consequences of cancer. Toll-free counseling hotline, educational pamphlets, newsletter, and referrals.

Cancer Care of New Jersey
141 Dayton Street
Ridgewood, NJ 07450
Tel: (201) 444-6630
E-mail: njinfo@cancercare.org
Web: <http://www.cancercare.org>
Provides counseling, information, and financial assistance to patients and families.

Cancer Control Society (CCS)
2043 North Berendo Street
Los Angeles, CA 90027
Tel: (323) 663-7801
Fax: (323) 663-7757
E-mail: cancercontrol@cox.net
Web: <http://www.cancercontrolsociety.com>
Educates health professionals and the public about preventing and controlling cancer and other diseases through many various methods.

Cancer Federation (CFI)
P.O. Box 1298
Banning, CA 92220-0009
Tel: (800) 207-2873
Fax: (909) 849-0156

E-mail: info@cancerfed.org
Web: <http://www.cancerfed.com>
Provided education and counseling for patients with cancer and their families.

Cancer Hope Network
Two North Rd., Suite A
Chester, NJ 07930
Tel: (877) HPE-NET
Fax: (908) 879-6518
E-mail: info@cancerhopenetwork.org
Web: <http://www.cancerhopenetwork.org>
Matches cancer patients and their families with trained volunteers who have undergone and recovered from a similar cancer experience.

Cancer Information and Counseling Line (CICL)
1600 Pierce St.
Denver, CO 80214
Tel: (800) 525-3777
E-mail: cicl@amc.org
Web: <http://www.amc.org/>
A toll-free telephone service for cancer patients, family members, friends, cancer survivors, and the general public. Education, short-term counseling, and referrals.

Cancer Survivors Network
Tel: (877) 333-HOPE
Web: <http://www.acscsn.org>
A telephone and Web-based service for cancer survivors, their families, caregivers, and friends.

Cancervive, Inc.
11636 Chayote St.
Los Angeles, CA 90049
Tel: (800) 4-TO-CURE
Fax: (310) 471-4618
E-mail: cancervivr@aol.com
Web: <http://www.cancervive.org>
Education, telephone counseling, referrals, and other services.

The Candlelighters Childhood Cancer Foundation
3910 Warner St.
P.O. Box 498
Kensington, MD 20895
Tel: (800) 366-2223
Fax: (301) 962-3521
E-mail: info@candlelighters.org
Web: <http://www.candlelighters. org>
Education and support for families of children with cancer.

Carcinoid Cancer Foundation (CCF)
333 Mamaroneck Avenue, No. 492
White Plains, NY 10605
Tel: (888) 722-3132
Fax: (914) 683-0183
E-mail: carcinoid@optonline.net
Web: <http://www.carcinoid.org/>
Provides information, support, and resources for health care providers and for patients.

Caring and Sharing Cancer Support Group
401 South Freeman Street
Oceanside, CA 92054-4002
Tel: (760) 439-4307
E-mail: oceansidepier@juno.com
Provides support for seniors only. Looks into needs of anyone affected by any form of cancer.

CATS - Survivors Assisting Your Head Injury (CATS SAY-HI!)
P.O. Box 80346
Lansing, MI 48908-0346
Tel: (517) 676-3992
E-mail: catstbi@voyager.net
Web: <http://www.catstbi.org>
Peer-led organization that provides support, education, information to survivors, friends, and communities for any head injury including tumors and other diseases and injuries.

Children's Blood Foundation (CBF)
333 East 38th, Room 830
New York, NY 10016
Tel: (212) 297-4336
Fax: (212) 297-4340
E-mail: info@childrensbloodfoundation.org
Web: <http://www.childrensbloodfoundation.org>
Provides support to total patient care facility at Cornell Medical Center and sponsors special social events.

Children's Hospice International
901 N. Pitt St., Suite 230
Alexandria, VA 22314
Tel: (703) 684-0330 or (800) 2-4-CHILD
E-mail: chiorg@aol.com
Web: <http://www.chionline.org>
Support network and resource clearinghouse for dying children and their families.

Colon Cancer Alliance
175 Ninth Avenue
New York, NY 10011
Tel: Office: (212) 627-7451
Tel: Toll Free Helpline: (877) 422-2030
Web: <http://www.ccalliance.org>

Colorectal Cancer Network
P.O. Box 182
Kensington, MD 20895-0182
Tel: (301) 879-1500
E-mail: ccnetwork@colorectal-cancer.net
Web: <http://www.colorectal-cancer.net>
Support groups, Internet chat room, hospital visitation programs, and a "One on One" service that connects newly diagnosed individuals with long-term survivors.

Corporate Angel Network (CAN)
Westchester County Airport
One Loop Road
White Plains, NY 10604
Tel: (914) 328-1313
Fax: (914) 328-3938
E-mail: info@corpangelnetwork.org
Web: <http://www.CorpAngelNetwork.org>
Arranges free flights for patients with cancer who must travel to and from recognized treatment centers. All who do not need onboard care are eligible.

Cure for Lymphoma Foundation
215 Lexington Ave.
New York, NY 10016-6023
Tel: (800) CFL-6848
E-mail: info@cfl.org
Web: <http://www.cfl.org>
Patient-to-patient telephone network, educational materials, research, and support.

CURE Childhood Cancer Association
200 Westfall Road
Rochester, NY 14620
Tel: (585) 473-0180
Fax: (585) 473-0201
E-mail: curekids@rochester.rr.com
Web: <http://curechildhoodcancer.org>
Provides support (financial, educational, and emotional) to families coping with cancer in a child.

Cure Research Foundation
P.O. Box 3782
Westlake Village, CA 91359
Tel: (805) 498-0185
Fax: (805) 498-4868
E-mail: ccf@cancure.org
Web: <http://www.cancure.org>
Dedicated to research and treatment in alternative cancer therapies. Also provides information on treatments and counseling services (where funded).

The Cutaneous Lymphoma Network
Attn; Judi Van Horn, R.N., Editor
c/o Department of Dermatology,
University of Cincinnati
P.O. Box 670523
Cincinnati, OH 45267-0523
Tel: (513) 558-6805

Produces a newsletter with articles on this cancer, information on support groups, and opportunities for contact with other mycosis fungoides patients.

Dana-Farber Cancer Institute
44 Binney Street
Boston, MA 02115
Tel: (617) 632-3000
E-mail: dana-farbercontact-us@dfci.harvard.edu
Web: <http://www.dfci.harvard.edu>
Dedicated to supporting children and adults with cancer.

Danville Cancer Association
1225 West Main Street
Danville, VA 24541
Tel: (434) 792-3700
Fax: (434) 791-3187
Supports cancer patients with supplies, equipment, transportation, and financial assistance. Also sponsors C.O.P.I.N.G. Cancer Support Group.

EyesOnThePrize.Org
446 S. Anaheim Hills Road, #108
Anaheim Hills, CA 92807
Web: <http://www.eyesontheprize.org>
On-line information and emotional support for women with gynecologic cancer.

Federation for Children with Special Needs
1135 Trumont St.
Boston, MA 02120
Tel: (800) 331-0688
Web: <http://www.fcsn.org>
Provides information, support, and assistance to parents of children with disabilities, their professional partners, and their communities.

Florida Brain Tumor Association
P.O. Box 770182-0182
Coral Springs, FL 3307-0182
Tel: (954) 755-4307
Fax: (954) 755-3206
E-mail: bt1diva@aol.com
Dedicated to support brain tumor survivors and their families and health care professionals.

Gilda's Club
322 Eighth Ave.
New York, NY 10001
Tel: (888) GILDA-4-U
Fax: (917) 305-0549
E-mail: info@gildasclub.org
Web: <http://www.gildasclub.org>
Support groups for children, teens and adults, lectures, workshops, networking groups, special events, and children's programs.

Gyn Cancer Network
c/o Cancer Action Inc.
255 Alexander Steet
Rochester, NY 14607
Tel: (716) 423-9700
Fax: (716) 423-9072
Web: <http://www.canceraction.org>
Dedicated to supporting women with gynecological cancer.

Gynecologic Cancer Foundation
401 North Michigan Avenue
Chicago, IL 60611
Tel: (800) 444-4441. (312) 644-6610.
Web: <http://www.wcn.org/gcf>
Research, education, and philanthropy for women with gynecologic cancer.

Hairy Cell Leukemia Research Foundation
2345 County Farm Lane
Schaumburg, IL 60194
Tel: (800) 693-6173
Web: <http://www.hairycellleukemia.org/>

HOPE Center for Cancer Support
297 Wickenden St.
Providence, RI 02903
Tel: (401) 454-0404
Fax: (401) 454-0411
E-mail: hope@hopecenter.net
Web: <http://www.hopecenter.org>

International Myeloma Foundation
12650 Riverside Dr., Suite 206
North Hollywood, CA 91607
Tel: (800) 452-CURE
Fax: (818) 487-7454
E-mail: theimf@myeloma.org
Web: <http://www.myeloma.org>
Support and treatment information for myeloma patients and their families.

International Waldenstrom's Macroglobulinemia Foundation
2300 Bee Ridge Road
Sarasota, FL 34239-6226
Tel: (941) 927-IWMF
Web: <http://www.iwmf.com>
Information, educational programs, support for patients and families, research support.

The Johns Hopkins Meningioma Society
Johns Hopkins University
Harvey 811
600 North Wolfe Street
Baltimore, MD 21205-8811
Tel: (410) 614-2886
Web: <http://www.meningioma.org>

Kidney Cancer Association
1234 Sherman Ave, Suite 203
Evanston, IL 60202
Tel: (800) 850-9132
Fax: (847) 332-2978
E-mail: office@kidneycancerassociation.org
Web: <http://www.kidneycancerassociation.org>
Supports research, offers printed materials about the diagnosis and treatment of kidney cancer, sponsors support groups, and provides physician referral information.

Lance Armstrong Foundation (LAF)
P.O. Box 161150
Austin, TX 78716-1150
Tel: (512) 236-8820
E-mail: livestrong@laf.org
Web: <http://www.laf.org>
Serves the public through advocacy, research, and education including LiveStrong (www.livestrong.org) a resource for people dealing with cancer.

Leukemia & Lymphoma Society
1311 Mamaroneck Ave.
White Plains, NY 10605
Tel: (800) 955-4572
Fax: (914) 949-6691
E-mail: infocenter@leukemia-lymphoma.org
Web: <http://www.leukemia-lymphoma.org/hm_lls>
Education, free materials, and various support services. Also sponsors research.

Life Raft Group (LRG)
555 Preakness Avenue, Level 2E, Suite 2
Totowa, NJ 07512
Tel: (973) 389-2070
Fax: (973) 389-2073
E-mail: liferaft@liferaftgroup.org
Web: <http://www.liferaftgroup.org>
Dedicated to providing support through information, research, and education for patients with Gastrointestinal Stromal Tumor (GIST).

Look Good. . .Feel Better
Tel: (800) 395-LOOK
Web: <http://www.lookgoodfeelbetter.org>
For adults and teens undergoing cancer treatment; offers techniques and assistance in improving physical appearance.

The Lymphoma Research Foundation of America, Inc.
8800 Venice Boulevard, Suite 207
Los Angeles, CA 90034

Tel: (800) 500-9976
Fax: (310) 204-7043
E-mail: lrf@lymphoma.org
Web: <http://www.lymphoma.org>
Supports research into treatments for lymphoma and provides educational and emotional support programs for patients and families.

Make Today Count (MTC)
1235 East Cherokee Street
Springfield, MO 65804-2203
Tel: (417) 885-2588
Fax: (417) 885-2587
E-mail: czimmerman@sprg.smhs.com;
Provides information, support, and resources to health professionals, patients, families, and friends.

Mothers Supporting Daughters with Breast Cancer (MSDBC)
21710 Bayshore Road
Chestertown, MD 21620
Tel: (410) 778-1982
Fax: (410) 778-1411
E-mail: msdbc@dmv.com
Web: <http://www.mothersdaughters.org>
Support for mothers of daughters who have been diagnosed with breast cancer.

Multiple Myeloma Research Foundation
51 Locust Avenue, No. 201
New Canaan, CT 06840-4739
Tel: (203) 972-1250
E-mail: themmrf@themmrf.org
Web: <http://www.multiplemyeloma.org>
Information for patients and families. Dedicated to raising awareness of the disease and funding research.

The Mycosis Fungoides Foundation
P.O. Box 374
Birmingham, MI, 48102-0374
Tel: (248) 644-9014
Web: <http://mffoundation.org>

National Alliance of Breast Cancer Organizations
9 East 37th St., 10th floor
New York, NY 10016
Tel: (888) 80-NABCO
Fax: (212) 689-1213.

National Association of Prostate Cancer Support Groups
P.O. Box 1253
Lakefield, Ontario K0L 2H0
Canada
Tel: (866) 810-CPCN
Fax: (705) 652-0663
E-mail: cpcn@nexicom.net
Web: <http://www.cpcn.org>

National Bone Marrow Transplant Link
20411 W. 12 Mile Rd., Suite 108
Southfield, MI 48076
Tel: (800) LINK-BMT (800-546-5268)
Web: <http://www.nbmtlink.org>
Web site provides publications about the logistics of bone marrow transplantation, information about the National Bone Marrow Transplant Link, and a peer support program.

National Brain Tumor Foundation (NBTF)
414 13th St., Suite 700
Oakland, CA 94612-2603
Tel: (510) 839-9777 or (800) 934-CURE
E-mail: nbtf@braintumor.org
Web: <http://www.braintumor.org>
Provides patients and their families with information on how to cope with brain tumors. National and regional conferences, printed materials, access to a national network of patient support groups, and answers to patient inquiries.

National Cancer Institute
9000 Rockville Pike, Building 31, Room 10A16
Bethesda, MD 20892
Tel: (800) 422-6237.
Web: <http://www.nci.nih.gov>

National Cervical Cancer Coalition (NCCC)
2625 Alcatraz Avenue, Suite 282
Berkley, CA 94705
Tel: (800) 685-5531. (818) 909-3849
Fax: (818) 780-9-8199
E-mail: info@nccc-online.org
Web: <http://www.nccc-online.org>
Information, education, access to screening and treatment, and support services; sponsors the Cervical Cancer Quilt Project.

National Childhood Cancer Foundation (NCCF)
440 E. Huntington Dr., Suite 402
P.O. Box 60012
Arcadia, CA 91066-6012
Tel: (800) 458-6223 or (626) 447-1674
Fax: (626) 447-6359
E-mail: info@nccf.org
Web: <http://www.curesearch.org/nccfintro.aspx>

National Children's Cancer Society (NCCS)
1015 Locust, Suite 600
St. Louis, MO 63101
Tel: (800) 532-6459
Fax: (314) 241-6949
E-mail: volunteers@children-cancer.com
Web: <http://www.nationalchildrenscancersociety.com>
Promotes children's health through financial and in-kind assistance, advocacy, support services, education and prevention programs.

National Children's Leukemia Foundation
172 Madison Ave.
New York, NY 10016
Tel: (212) 686-2722 or (800) GIVE-HOPE
Fax: (212) 686-2750
Web: <http://www.leukemiafoundation.org>
Support network, bone marrow search, patient advocacy, education, and dream fulfillment.

National Coalition for Cancer Survivorship (NCCS)
1010 Wayne Ave., Suite 770
Silver Spring, MD 20910-5600
Tel: (877) 622-7937
Fax: (301) 565-9670
E-mail: info@canceradvocacy.org
Web: <http://www.canceradvocacy.org>
A network for cancer support, advocacy, and quality of life issues.

National Comprehensive Cancer Network (NCCN)
500 Old York Road, Suite 250
Jenkintown, PA 19046
Tel: (215) 690-0300
Fax: (215) 690-0280
E-mail: information@nccn.org
Web: <http://www.nccn.org>

National Kidney Foundation
30 East 33rd St.
New York, NY 10016.
Tel: (800) 622-9010
Web: <http://www.kidney.org>

National Organization for Rare Disorders
100 Route 37
PO Box 8923
New Fairfield, CT 06812
Tel: (203) 746-6518
Web: <http://www.rarediseases.org>
The National Organization for Rare Disorders (NORD) is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service. NORD also provides referrals to additional sources of assistance and ongoing support.

National Ovarian Cancer Coalition (NOCC)
500 NE Spanish River Blvd., Suite 8
Boca Raton, FL 33431
Tel: (561) 393-0005 or (888) OVAR-IAN
Fax: (561) 393-7275
E-mail: NOCC@ovarian.org
Web: <http://www.ovarian.org>
Referral, support, educational materials, and a database of gynecologic oncologists searchable by state.

National Pancreas Foundation
PO Box 935
Wexford, PA 15090-0935
Web: <http://www.pancreasfoundation.org>
The National Pancreas Foundation (NPF) was created to initiate and foster the pursuit of medical advancements in pancreatic disease research, as well as to develop a support network for all individuals suffering from pancreatic disorders.

National Retinoblastoma Parents Group
P.O. Box 317
Watertown, MA 02471
Tel: (800) 562-6265
Fax: (617) 972-7444
E-mail: napvi@perkins.pvt.k12.ma.us

Neurofibromatosis (NF)
9320 Annapolis Road, Suite 300
Lanham, MD 20706-3123
Tel: (301) 918-4600
Fax: (301) 918-0009
E-mail: nfinfo@nfinc.org
Web: <http://www.nfinc.org>
Provides support for individuals with NF and for their families, health care providers and others.

Nevoid Basal Cell Carcinoma Syndrome Support Network
162 Clover Hill Street
Marlboro, MA 01752
Tel: (800) 815-4447.
E-mail: souldansur@aol.com
Web: <http://bccns.org/nbccs.htm/>

Nevus Outreach
1601 Madison Boulevard
Bartlesville, OK 74006
Tel: (918) 331-0595
Web: <http://www.nevus.org/>
Discussion groups, chat rooms, message board, and online services for patients with Biant Nevi and Neurocutaneous Melanosis.

OncoChat IRC Channel
Web: <http://www.oncochat.org>
Online peer support for cancer survivors, family, and friends.

Pancreatic Cancer Action Network (PanCAN)
P.O. Box 1010
Torrance, CA 90505
Tel: (877) 2-PANCAN
E-mail: information@pancan.org
Web: <http://www.pancan.org>
Advocacy, education, support links, and a survivorship forum.

Patient Advocate Foundation
753 Thimble Shoals Blvd, Suite B
Newport News, VA 23606
Tel: (800) 532-5274
Fax: (757) 873-8999
Web: <http://www.patientadvocate.org/>
Serves as an active liaison between the patient and their insurer, employer and/or creditors to resolve insurance, job discrimination and/or debt crisis matters relative to their diagnosis through case managers, doctors and attorneys. Seeks to safeguard patients through effective mediation assuring access to care, maintenance of employment and preservation of their financial stability.

R. A. Bloch Cancer Foundation, Inc.
4400 Main St.
Kansas City, MO 64111
Tel: (800) 433-0464
Fax: (816) 931-7486
E-mail: hotline@hrblock.com
Web: <http://www.blochcancer.org>
Matches newly diagnosed cancer patients with trained, home-based volunteers who have been treated for the same type of cancer. Offers informational materials, including a multidisciplinary list of institutions that offer second opinions.

Reach to Recovery
c/o American Cancer Society
1599 Clifton Road2454
P.O. Box 102454
Atlanta, GA 30368
Tel: (800) ACS-2345
Web: < http://www.cancer.org/eprise/main/docroot/shr/content/shr_2.1_x_reach_to_recovery? sitearea=shr>
Trained volunteers provide support and information for patients, families, and loved onew with breast cancer.

Ronald S. Hirshberg Pancreatic Cancer Information and Advocacy Center
375 Homewood Rd.
Los Angeles, CA 90049.
Tel: (310) 472-6310.
Web: <http://www.pancreatic.org>
Provides informative booklets and other educational materials about pancreatic cancer, and offers referrals to support groups and other organizations.

San Francisco AIDS Foundation (SFAF)
995 Market Street, #200
San Francisco, CA 94103
Tel: (415) 487-3000 or (800) 367-AIDS
Fax: (415) 487-3009
Web: <http://www.sfaf.org>

Sarcoma Alliance
775 East Blithedale #334
Mill Valley, CA 94941
Tel: (415) 381-7236
E-mail: info@sarcomaalliance.org
Web: <http://www.sarcomaalliance.org>

Skin Cancer Foundation
245 Fifth Ave., Suite 1403
New York, NY 10016
Tel: (800) SKIN-490
Fax: (212) 725-5751
E-mail: info@skincancer.org
Web: <http://www.skincancer.org>

Spinal Cord Tumor Support
Web:<http://www.spinalcordtumor.homestead.com>

STARBRIGHT Foundation
11835 W. Olympic Blvd., Suite 500
Los Angeles, CA 90064
Tel: (310) 479-1212
Fax: (310) 479-1235
E-mail: ford@starbright.org
Web: <http://www.starbright.org>
Creates projects and materials that are designed to help seriously ill children and adolescents cope with the psychosocial and medical challenges they face.

Support for People with Oral and Head and Neck Cancer (SPOHNC)
P.O. Box 53
Locust Valley, NY 11560-0053
Tel: (800) 377-0928
Web: <http://www.spohnc.org>

United Ostomy Association, Inc.
19772 MacArthur Blvd., Suite 200
Irvine, CA 92612-2405
Tel: (800) 826-0826
E-mail: uoa@deltanet.com
Web: <http://www.uoa.org>
Assists ostomy patients through mutual aid and emotional support, provides information to patients and the pub-

lic, and sends volunteers to visit with new ostomy patients.

US TOO! International, Inc.
5003 Fairview Ave.
Downers Grove, IL 60515
Tel: (800) 80-US-TOO
E-mail: ustoo@ustoo.com
Web: <http://www.ustoo.org>
A support group organization for cancer patients.

Vital Options and "The Group Room" Cancer Radio Talk Show
15060 Ventura Blvd., Suite 211
Sherman Oaks, CA 91403
Tel: (800) GRP-ROOM
E-mail: geninfo@vitaloptions.org
Web: <http://www.vitaloptions.org>
Vital Options holds a weekly syndicated call-in cancer radio talk show called "The Group Room," a forum for patients, long-term survivors, family members, physicians, and therapists to discuss cancer issues; also simulcast on the Internet.

The Wellness Community
35 E. Seventh St., Suite 412
Cincinnati, OH 45202
Tel: (513) 421-7111 or (888) 793-WELL
E-mail: help@wellness-community.org
Web: <http://www.wellness-community.org>
Support groups, stress reduction and cancer education workshops, nutrition guidance, exercise sessions, and social events.

Women's Cancer Resource Center
4604 Chicago Ave. South
Minneapolis, MN 55407
Tel: (877) 892-6742
Fax: (612) 822-4784
E-mail: wcrc@mr.net
Web: <http://www.givingvoice.org>
Education, support, special programs, advocacy.

Y-ME National Breast Cancer Organization, Inc.
212 W. Van Buren St., Suite 500
Chicago, IL 60607
Tel: (312) 986-8338 or (800) 221-2141
Fax: (312) 294-8598
E-mail: bparker@y-me.org
Web: <http://www.y-me.org>
Open-door groups, 24-hour hotline, early detection workshops, and support programs. Numerous local chapter offices located throughout the United States.

APPENDIX III: GOVERNMENT AGENCIES AND RESEARCH GROUPS

Agency for Healthcare Research and Quality
2101 E. Jefferson St., Suite 501
Rockville, MD 20852
Tel: (301) 594-1364
Web: <http://www.ahcpr.gov>
Conducts and supports research and provides information for the health care consumer

American Association for Cancer Research
Public Ledger Bldg., Suite 826
150 S. Independence Mall West
Philadelphia, PA 19106-3483
Tel: (215) 440-9300
Fax: (215) 440-9313
Web: <http://www.aacr.org>

American Brachytherapy Society (ABS)
12100 Sunset Hills Road, #130
Reston, VA 20190
Tel: (703) 234-4078
Fax: (703) 435-4390
Web: <http://www.americanbrachytherapy.org>

American Brain Tumor Association (ABTA)
2720 River Road, Suite 146
Des Plaines, IL 60018
Tel: (847) 827-9910
Fax: (847) 827-9918
E-mail: info@abta.org
Web: <http://hope.abta.org/site/PageServer>

American Cancer Society
2200 Century Parkway, Suite 950
Atlanta, GA 30345
Tel: (800) ACS-2345
Fax: (404) 315-9348
Web: <http://www.cancer.org>

American Foundation for Urologic Disease (AFUD)
1000 Coprorate Boulevard, Suite 410
Linthicum, MD 21090
Tel: (410) 689-3990
Fax: (410) 689-3998
E-mail: admin@afud.org
Web: <http://www.afud.org>

American Head and Neck Society (AHNS)
c/o Paul A. Levine, Pres.
11300 West Olymic Boulevard, Suite 600
Los Angeles, CA 90064
Tel: (310) 437-0559
Fax: (310) 437-0585
E-mail: pal@virginia.edu
Web: <http://www.headnadneckcancer.org>

American Headache Society (AHS)
19 Mantua Road
Mount Royal, NJ 08061
Tel: (856) 423-0043
Fax: (856) 423-0082
E-mail: ahshq@talley.com
Web: <http://www.ahsnet.org>

American Institute for Cancer Research
1759 R St. NW
Washington, DC 20009
Tel: (800) 843-8114
Fax: (202) 328-7226
E-mail: aicrweb@aicr.org
Web: <http://www.aicr.org>
Charity and research organization that focuses on diet and nutrition as they relate to the prevention and treatment of cancer.

American Lung Association (ALA)
61 Broadway, 6th Floor
New York, NY 10006
Tel: (800) LUNGUSA
Fax: (212) 315-8872
E-mail: info@lungusa.org
Web: <http://www.lungusa.org>
Promotes research, education, and advocacy for prevention of lung disease.

American Radium Society (ARS)
53 West Jackson Boulevard, Suite 663
Chicago, IL 60604
Tel: (312) 322-0730
Fax: (312) 322-0732
E-mail: info@americanradiumsociety.org
Web: <http://www.americanradiumsociety.org>

American Society for Therapeutic Radiology and Oncology (ASTRO)
12500 Fair Lakes Circle, Suite 375
Fairfax, VA 22033-3882
Tel: (703) 502-1550
Fax: (703) 502-7852
E-mail: webmaster@astro.org
Web: <http://www.astro.org>

American Society of Breast Disease (ASBD)
P.O. Box 140186
Dallas, TX 75214
Tel: (214) 368-6836
Fax: (214) 368-5719
E-mail: info@asbd.org
Web: <http://www.asbd.org>

American Society of Clinical Oncology (ASCO)
1900 Duke Street, Suite 200
Alexandria, VA 22314
Tel: (703) 299-0150
Fax: (703) 2991044
E-mail: asco@asco.org
Web: <http://www.asco.org>

American Society of Cytopathology (ASC)
400 West Ninth Street, Suite 201
Wilmington, DE 19801

Tel: (302) 429-8802
Fax: (302) 429-8807
E-mail: asc@cytopathology.org
Web: <http://www.cytopathology.org>

American Society of Pediatric Hematology/Oncology (ASPHO)
4700 West Lake Avenue
Glenview, IL 60025-1485
Tel: (847) 375 4716
Fax: (877) 734-9557
E-mail: info@aspho.org
Web: <http://www.aspho.org>

American Society of Preventive Oncology (ASPO)
256 WARF Building
610 Walnut Street
Madison, WI 53705
Tel: (608) 263-9515
Fax: (608) 263-4497
E-mail: hasahel@facstaff.wisc.edu
Web: <http://www.aspo.org>

Association for Research of Childhood Cancer (AROCC)
P.O. Box 251
Buffalo, NY 14225-0251
Tel: (716) 681-4433
E-mail: odonnell@msn.org
Web: <http://www.arocc.org>

Association of American Cancer Institutes (AACI)
200 Lothrop Street
Iroquois Building, #308
Pittsburgh, PA 15213
Tel: (412) 647-2076
Fax: (412) 647-3659
E-mail: mail@aaci-cancer.org
Web: <http://www.aaci-cancer.org>

Association of Cancer Executives (ACE)
475 South Frontage Road, Suite 101
Burr Ridge, IL 60527
Tel: (630) 323-1170
Fax: (630) 323-6989
E-mail: info@cancerexecutives.org
Web: <http://www.cancerexecutives.org>

Association of Community Cancer Centers(ACCC)
11600 Nebel Street, Suite 201
Rockville, MD 20852
Tel: (301) 984-9496
Fax: (301) 770-1949
Web: <http://www.accc-cancer.org>

Breast Cancer Alliance
15 East Putnam Avenue
Box 414
Greenwich, CT 06831-3301
Tel: (203) 861-0014
Fax: (203) 861-1940
E-mail: info@breastcanceralliance.org
Web: <http://www.breastcanceralliance.org>

Cancer Control Society (CCS)
2043 North Berendo Street
Los Angeles, CA 90027
Tel: (323) 663-7801
Fax: (323) 663-7757
E-mail: cancercontrol@cox.net
Web: <http://www.cancercontrolsociety.com>

Cancer Federation (CFI)
P.O. Box 1298
Banning, CA 92220-0009
Tel: (909) 849-4325
Fax: (909) 849-0156
E-mail: info@cancerfed.org
Web: <http://www.cancerfed.com>

Cancer Research Foundation of America
1600 Duke Street, Suite 500
Alexandria, VA 22314
Tel: (703) 836-4412
Fax: (703) 836-4413
E-mail: info@preventcancer.org
Web: <http://www.preventcancer.org>

Cancer Treatment Research Foundation
3150 Salt Creek Lane, Suite 118
Arlington Heights, IL 60005-1090
Tel: (888) 221-CTRF
Web: <http://www.ctrf.org>

Carcinoid Cancer Foundation
1751 York Ave.
New York, NY 10128
Tel: (888) 722-3132
Fax: (914) 683-5919
Web: <http://www.carcinoid.org>
Research support, news, and education.

Centers for Disease Control and Prevention
1600 Clifton Rd.
Atlanta, GA 30333
Tel: (800) 311-3435
Web: <http://www.cdc.gov>
Develops and applies disease control, environmental health, and health promotion and education. Operates the Cancer Control and Prevention program and the Tobacco Information and Prevention Source (TIPS).

Chemotherapy Foundation (CF)
183 Madison Avenue, Room 403
New York, NY 10016
Tel: (212) 213-9292
Fax: (212) 213-3831
E-mail: scox@chemotherapyfoundation.org

Children's Blood Foundation (CBF)
333 East 38th, Room 830
New York, NY 10016
Tel: (212) 297-4336
Fax: (212) 297-4340
E-mail: info@childrensbloodfoundation.org
Web:<http://www.childrensbloodfoundation.org>

Children's Leukemia Research Association (NLA)
585 Stewart Avenue, Suite LL18
Garden City, NY 11530
Tel: (516) 222-1944
Fax: (516) 222-0457
E-mail: info@childrensleukemia.org
Web: <http://www.childrensleukemia.org>

City of Hope National Medical Center (COH)
1500 East Duarte Road
Duarte, CA 91010
Tel: (626) 359-8111
Fax: (626) 301-8115
E-mail: egoehner@coh.org
Web: <http://www.cityofhope.org>

Coleman Foundation
575 West Madison Street, Suite 4605
Chicago, IL 60661
Tel: (312) 902-7120
Fax: (312) 902-7124
E-mail: coleman@colemanfoundation.org
Web: <http://www.colemanfoundation.org>

Concern Foundation
8383 Wilshire Boulevard, Suite 337
Beverly Hills, CA 90211
Tel: (310) 724-5333
Fax: (310) 858-1474
E-mail: info@concernfoundation.org
Web: <http://www.concernfoundation.org>

Cure Research Foundation
P.O. Box 3782
Westlake Village, CA 91359
Tel: (805) 498-0185
Fax: (805) 498-4868
E-mail: ccf@cancure.org
Web: <http://www.cancure.org>
Dedicated to research and treatment in alternative cancer therapies.

CuresNow
1710 North Vermont Avenue, Suite 102
Los Angeles, CA 90027
Tel: (323) 660-6362
Fax: (310) 244-1480
E-mail: act@curesnow.org
Web: <http://www.curesnow.org>
Dedicated to research in regenerative medicine.

Cystic Fibrosis Foundation
6931 Arlington Road
Bethesda, MD 20814
Tel: (301) 951-4422
Fax: (301) 951-6378
E-mail: info@cff.org
Web: <http://www.cff.org>
Dedicated to supporting research, professional education, and care centers for patients with cystic fibrosis.

Damon Runyon Cancer Research Foundation
675 3rd Avenue, 25 Floor
New York, NY 10017
Tel: (212) 455-0500
Fax: (212) 455-0509
E-mail: info@drcrf.org
Web: <http://www.cancerresearchfund.org/>
Dedicated to advancing cancer research through various monetary awards.

Friends of Cancer Research
3299 K. Street, NW, Suite 100
Washington, DC 20007
Tel: (202) 944-6711
Fax: (202) 333-7840
E-mail: info@focr.org
Web: <http://www.focr.org>

Institutos Nacionales de la Salud (National Institutes of Health Hispanic Communications Initiative)
<http://salud.nih.gov>
A Spanish-language health information Web site.

International Myeloma Foundation
12650 Riverside Dr., Suite 206
North Hollywood, CA 91607
Tel: (818) 487-7455
Fax: (818) 487-7454
E-mail: theimf@myeloma.org
Web: <http://www.myeloma.org>

International Oncology Study Group (IOSG)
4515 Verone
Bellaire, TX 77401
Tel: (713) 432-7229
Promotes clinical therapeutic research.

Kidney Cancer Association
1234 Sherman Ave, Suite 203
Evanston, IL 60202
Tel: (847) 332-1051
Fax: (847) 332-2978
E-mail: office@kidneycancerassociation.org
Web: <http://www.kidneycancerassociation.org>
Supports research, offers printed materials about the diagnosis and treatment of kidney cancer, sponsors support groups, and provides physician referral information.

Leukemia & Lymphoma Society
1311 Mamaroneck Ave.
White Plains, NY 10605
Tel: (914) 949-5213
Fax: (914) 949-6691
E-mail: infocenter@leukemia-lymphoma.org
Web: <http://www.leukemia-lymphoma.org>
Education, free materials, and various support services. Also sponsors research.

Life Raft Group (LRG)
555 Preakness Avenue, Level 2E, Suite 2
Totowa, NJ 07512
Tel: (973) 389-2070
Fax: (973) 389-2073
E-mail: liferaft@liferaftgroup.org
Web: <http://www.liferaftgroup.org>
Dedicated to providing support through information, research, and education for patients with Gastrointestinal Stromal Tumor (GIST).

Lymphoma Research Foundation (LRF)
8800 Venice Boulevard, Suite 207
Los Angeles, CA 90034
Tel: (310) 204-7040
Fax: (310) 204-7043
E-mail: lrf@lymphoma.org
Web: <http://www.lymphoma.org>

Melanoma Research Foundation (MRF)
24 Old Georgetown Road
Princeton, NJ 08540
Tel: (800) MRF-1290
Fax: (732) 821-5955
E-mail: mrf@melanoma.org
Web: <http://www.melanoma.org>

Multiple Myeloma Research Foundation (MMRF)
51 Locust Avenue, #201
New Canaan, CT 06840-4739
Tel: (203) 972-1250
E-mail: themmrf@themmrf.org
Web: <http://www.multiplemyeloma.org>

National Association for Proton Therapy
1301 Highland Drive
Silver Spring, MD 20910
Tel: (301) 587-6100
Fax: (301) 913-0372
E-mail: lenarzt@verizon.net
Web: <http://www.proton-therapy.org>

National Breast Cancer Coalition (NBCC)
1707 L Street NW, Suite 1060
Washington, DC 20036
Tel: (202) 296-7477
Fax: (202) 265-6854
E-mail: info@natlbcc.org
Web: <http://www.stopbreastcancer.org>
Promotes research into the cause, treatments and cures for breast cancer.

National Cancer Center (NCC)
88 Sunnyside Boulevard, Suite 307
Plainview, NY 11803
Tel: (516) 349-0610
Fax: (516) 349-1755
E-mail: info@nationalcancercenter.org
Supports educational programs and cancer research.

National Cancer Institute, National Institutes of Health
31 Center Dr., MSC 2580
Bethesda, MD 20892
Tel: (800) 4-CANCER
TTY: (800) 332-8615
Web: <http://www.nci.nih.gov>

National Center for Complementary and Alternative Medicine (NCCAM)
P.O. Box 8218
Silver Spring, MD 20907-8218
Tel/TTY: (888) 644-6226
Fax: (301) 495-4957
Web: <http://nccam.nih.gov>
Conducts research and provides information on the safety and effectiveness of complementary and alternative therapies.

National Coalition for Cancer Research (NCCR)
426 C St. NW
Washington, DC 20004
Tel: (202) 544-1880
Fax: (202) 543-2565
E-mail: md@capitolassociates.com
Web: <http://www.cancercoalition.org>

Advocacy group for cancer survivors and researchers—tracks cancer research and monitors legislation and funding.

National Foundation for Cancer Research
4600 W. West Highway, Suite 525
Bethesda, MD 20814
Tel: (800) 321-2873
Fax: (301) 654-5824
E-mail: sdeane@nfcr.org
Web: <http://www.nfcr.org/>

National Women's Cancer Research Alliance (NWCRA)
The Entertainment Industry Foundation
11132 Ventura Blvd., Suite 401
Studio City, CA 91604
Tel: (888) 87-NWCRA
Fax: (818) 760-7898
Web: <http://www.nwcra.org/>

Office of Research on Minority Health
6707 Democracy Blvd., Suite 800
MSC 5465
Bethesda, MD 20892-5465
Tel: (301) 402-1366
Fax: (301) 480-4049
Web: <http://www.ncmhd.nih.gov/>

Pediatric Cancer Research Foundation
18 Technology Dr., Suite 147
Irvine, CA 92618
Tel: (949) 727-7483
Fax: (949) 727-9501
E-mail: admin@pcrf-kids.com
Web: <http://www.pcrf.com>

The Pediatric Oncology Branch of the National Cancer Institute
Tel: (877) 624-4878 or (301)496-4256.
Web: <http://home.ccr.cancer.gov/oncology/pediatric/>.

U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-0001
Tel: (888) INFO-FDA
Web: <http://www.fda.gov/cder/cancer/index.htm>
Contains an Oncology Tools section with information on cancer and approved cancer drugs, oncology reference tools, and other resources.

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