

FEATURE STORY

About Cancer: Cancer Therapies

An easy-to-understand explanation of the various types of cancer treatment

As scientists learn more about cancer's biology and how it affects each patient, better methods have become available to treat cancer and prevent recurrence. This overview covers the types of therapy you may receive, including some new ones that have become available only during the past few years.

Surgery

If the cancer has not spread, surgical removal of most tumors is almost always necessary, and may require complete removal of the affected organ. Less invasive and less extensive methods are available in some cases, including laparoscopic surgery or lumpectomy as opposed to mastectomy (removing tumor tissue and a margin of surrounding healthy tissue compared with removing the entire breast).

VARIOUS TYPES OF CANCER SURGERY INCLUDE:

Laparoscopic surgery is performed through one or more small incisions that allow a thin fiberoptic scope, called a laparoscope, and specially designed surgical instruments to be inserted into the abdomen to remove the tumor. If the procedure is done in the chest cavity, it's called a thoracoscopy. Disease-free survival and recurrence rates for many types of cancer seem to be about the same when compared with traditional open surgery. The main benefits are faster recovery times, shorter hospital stays, and less risk of complications.

Robotic surgery, a newer modern approach, may have even more benefits for today's patient. As with laparoscopic surgery, the operation is done through a few small incisions. But instead of holding the surgical instruments, the surgeon sits at a control panel and moves the instruments with the aid of very precise robotic arms. Currently, the only surgical robot approved by the Food and Drug Administration is the da Vinci Surgical System. In addition to prostatectomy, the da Vinci system can be used for hysterectomy to treat cervical and endometrial cancer, gastric bypass, and mitral valve repair. The robot can also be used for some bladder and kidney cancers.

Radiofrequency ablation, or RFA, has emerged as a promising therapy for patients unable to undergo surgical resection. For this outpatient procedure, a thin needle-like probe is inserted into the tumor, and the tip is heated to destroy tumor cells. It can be used in combination with chemotherapy and radiation therapy. **Cryoablation** is a similar procedure that uses rapid freezing and thawing to kill the cancer cells.

Radiation Therapy

Radiation therapy is occasionally used alone in the treatment of some cancers, such as prostate or cervical cancer, but is most often used in combination with other therapies for many cancer types. In addition, radiation can be used to improve the cure rate following surgery, to allow less aggressive surgery, or to relieve side effects of advanced or incurable cancer. High doses of radiation may cause side effects after treatment as well as secondary cancers, so newer techniques target radiation more accurately to tumor sites in order to minimize these effects.

[View Illustration: Radiation Manipulation](#)

VARIOUS TYPES OF TARGETED RADIATION THERAPY INCLUDE:

Brachytherapy involves radiating the tumor directly from implanted radioactive seeds or wires implanted near the tumor site. Brachytherapy is used in prostate cancer, cervical cancer, and some other cancers. For breast cancer, partial breast irradiation (PBI) can be accomplished by brachytherapy within the lumpectomy cavity using a balloon catheter. PBI is increasingly being used for smaller lymph node-negative breast cancers and can be done in a few days instead of the usual six weeks.

Conformal radiotherapy employs several weak beams of radiation originating from different angles that intersect to produce a concentrated high dose of radiation at the tumor site. Intensity-modulated radiation therapy (IMRT) is an advanced type of conformal radiotherapy that uses multiple beams with varying intensity.

Stereotactic radiosurgery is another treatment option that utilizes radiation. Gamma Knife, for example, uses a computer to simultaneously focus about 200 small beams onto a tumor. The treatment is usually done once, and the patient's skull must be anchored to a specialized helmet to maintain positioning during the procedure. A similar technique, known as CyberKnife, bypasses the need for the helmet by instead using real-time imaging to make adjustments. Gamma Knife is used for small- to medium-sized tumors, while CyberKnife is typically employed for larger lesions.

Proton beam therapy is a newer form of radiation therapy that uses positively charged particles called protons that only travel a certain distance, as opposed to intense X-ray beams, called photons, used in conventional radiation. The method allows doctors to control the depth of radiation more precisely and deliver more

of it to tumors, while sparing nearby healthy tissue. Proton beam therapy is now used to treat some childhood cancers and some prostate, brain, lung, esophageal, and head and neck cancers. Although side effects are still possible, they are considerably less intense than with conventional radiation and are far less likely to be long-term. Currently, only a handful of proton beam radiation centers are open in the United States, but more are scheduled to open during the next two years.

Chemotherapy

Several types of chemotherapy, each with its own mechanism of action and side effects, are available for cancer. Many new drugs have greater efficacy and less toxicity than first-generation chemotherapy from 50 years ago. But much of the improvement in efficacy and toxicity resulted from a greater knowledge about how to deliver these drugs, including optimal dose and frequency of dose, alone and in combination.

Chemotherapy is used in several ways. It can be given as the primary—or main—treatment for some cancers, such as lymphoma and leukemia. Oncologists have also discovered chemotherapy given after surgery, known as adjuvant therapy, can in some cases improve survival and delay or prevent disease progression. Neoadjuvant chemotherapy is given before surgery, and often shrinks tumors enough to permit less extensive operations. In situations when cancer is not curable, palliative chemotherapy can often reduce symptoms caused by tumors.

BELOW ARE SOME OF THE MOST COMMONLY USED CLASSES OF CHEMOTHERAPY AGENTS:

Mitotic inhibitors disrupt mitosis, a phase of cell division when a cell duplicates and separates the chromosomes in its cell nucleus. Mitotic inhibitors include taxanes, such as Taxol (paclitaxel) and Taxotere (docetaxel), and a class of drugs called vinca alkaloids, including Velban (vinblastine), Oncovin (vincristine), and Navelbine (vinorelbine). They are used to treat several solid tumors, lymphomas, and leukemias. A new class of mitotic inhibitors, the epothilones, includes Ixempra (ixabepilone), which was approved in 2007 to treat advanced breast cancer in cases where taxanes no longer work. Mitotic inhibitors are known for their potential to cause peripheral nerve injury (neuropathy), which causes numbness and can be a dose-limiting side effect.

Alkylating agents are active against blood-related cancers, such as non-Hodgkin lymphoma, Hodgkin disease, chronic leukemias, and multiple myeloma, but are also effective in breast, ovarian, lung, and some gastrointestinal cancers. Some examples include cisplatin, carboplatin, Eloxatin (oxaliplatin), Cytoxan (cyclophosphamide), Ifex (ifosfamide), and Treanda (bendamustine). Alkylating agents work by damaging the DNA of cancer cells to prevent them from dividing and multiplying.

Antimetabolites are in a class of drugs that interfere with DNA and RNA production in cells. Common examples include Gemzar (gemcitabine), 5-FU (fluorouracil), Xeloda (capecitabine), Cytosar-U (cytarabine), and Alimta

(pemetrexed). These agents are only effective in a specific cycle of cell growth and are used to treat leukemia and cancers of the ovary, breast, gastrointestinal tract, and lung.

Topoisomerase I inhibitors, such as Camptosar (irinotecan) and Hycamtin (topotecan), interfere with enzymes that are important for accurate DNA replication. They are used to treat certain types of leukemia, as well as lung, ovarian, gastrointestinal, and other cancers.

Anthracyclines are anti-tumor antibiotics that interfere with enzymes, including topoisomerase II, involved in DNA replication. These agents treat a variety of tumors and work in all phases of the cell cycle. A major consideration when giving these drugs is the toxic effects they can have on the heart muscle. For this reason, lifetime dose limitations are often placed on these drugs. Adriamycin (doxorubicin), Ellence (epirubicin), and Daunomycin (daunorubicin) are the more commonly used anthracyclines.

Stem Cell Transplant

Referred to as bone marrow transplantation for many years, the term used today is hematopoietic stem cell transplantation. Bone marrow, the spongy material inside the bone, is the natural home for hematopoietic stem cells, which are the parental cells that develop into different types of blood cells, and a few of these cells find their way into the bloodstream. Today, these stem cells are more often harvested from the blood using “apheresis” machines, or even from umbilical cord blood from newborns.

Stem cell mobilizers, drugs that move stem cells from the bone marrow into the circulating blood, allow for better and faster collection of stem cells for transplantation. Mozobil (plerixafor), a drug approved in late 2008, is now used in some patients with non-Hodgkin lymphoma and multiple myeloma before transplant. Patients with leukemia, myeloma, low-grade lymphoma, myelodysplastic syndromes, and, less often, various other cancers, may be treated with a stem cell transplant.

High doses of chemotherapy and/or radiation have the unwanted side effect of damaging a patient’s bone marrow stem cells. Thus, stem cell transplants “rescue” patients from this high-dose treatment. Returning stem cells from the patient’s own body after high-dose treatment is known as an **autologous transplant**. Transplantation of stem cells from a related or unrelated donor whose tissue type matches that of the patient is called **allogeneic transplant**.

View Illustration: Types of Stem Cell Transplant

If the cells are taken from the patient, they are frozen and stored for later use. If the stem cells are obtained from a donor, they are usually infused in the patient soon after collection and may not need to be frozen. The cells find their way to the bone marrow, where they divide and mature into cells normally produced by healthy bone marrow in a process known as engraftment.

Graft-versus-host disease, or GVHD, may occur after allogeneic transplants when the donor immune cells view the recipient's body as foreign. The recipient's immune system has largely been destroyed by conditioning treatment and cannot fight back. The donor immune cells may attack certain organs (most often the skin and liver), which impairs the organs' ability to function and increases the chance of infection.

Acute GVHD occurs 10 to 70 days after a transplant, though the average time is around 25 days. About one-third to half of allogeneic transplant recipients develop acute GVHD, which can be serious and sometimes fatal. However, a small amount of GVHD can actually be helpful since the transplanted immune cells can also attack residual cancer cells.

Hormonal Therapy

Hormonal therapies interfere with the way sex hormones (androgens and estrogens) interact with certain types of tumors, particularly prostate and breast, and can be used alone or as adjuvant therapy.

Following surgery, women with hormone-dependent breast cancer—cancer fueled by estrogen—are commonly treated with **tamoxifen** and/or newer drugs called **aromatase inhibitors**, which include Femara (letrozole), Arimidex (anastrozole), and Aromasin (exemestane), to lower the risk of the cancer returning. These drugs are taken for at least five years, although the optimal length of time to give them is not yet known. These drugs are also used to treat advanced hormone-dependent breast cancers.

Aromatase inhibitors work by blocking an enzyme responsible for producing small amounts of estrogen in postmenopausal women. Since they cannot stop the ovaries of premenopausal women from producing estrogen, aromatase inhibitors are only effective in postmenopausal women.

Prostate cancer patients may receive **androgen deprivation therapy**, such as luteinizing hormone-releasing hormone (LHRH) analogs and LHRH antagonists, to lower testosterone levels. Another group of drugs, known as anti-androgens, are sometimes helpful if other drugs are no longer effective on their own.

Surgery can also quickly reduce the levels of sex hormones by removing the ovaries or testicles. While these operations are effective, work quickly, and are often less expensive than long-term use of drugs, they are permanent, and some people choose not to have these operations.

Biological Therapy

As researchers learn more about the specific molecular changes responsible for the abnormal growth and spread of cancer cells, they develop new drugs that target cancer cells more specifically than traditional chemotherapy. However, many of these newer agents must be combined with traditional chemotherapy, and they carry their own side effects, such as rash, heart damage, or high blood

pressure.

Scientists are now using biological, or targeted, agents not based on the type of cancer, but based on proteins or the status of certain genes contained in the tumor.

VARIOUS TYPES OF BIOLOGICAL THERAPY INCLUDE:

Monoclonal antibodies were among the first targeted agents. In 1975, British researchers figured out how to mass produce antibodies of a single (mono) type in the laboratory. At first, these “monoclonal” antibodies, sometimes abbreviated as MoAbs or MAbs, were made entirely by mouse cells, so the human immune system recognized them as foreign and mounted a response against them, possibly causing allergic-type reactions.

In the long term, this means the body’s immune system is primed to destroy them before they can be helpful. Over time, researchers learned how to replace some parts of these mouse antibody proteins with human parts. Some MAbs are now fully human and are likely to be safer and more effective than older MAbs. An even newer approach uses fragments of antibodies instead of whole ones to better reach a tumor.

In the past 10 years or so, the Food and Drug Administration approved several MAbs for the treatment of cancer, including Rituxan (rituximab) for non-Hodgkin lymphoma, Herceptin (trastuzumab) for HER2-positive breast cancer, Erbitux (cetuximab) for advanced colorectal and head and neck cancers, and Vectibix (panitumumab) for advanced colorectal cancer. Zevalin (ibritumomab tiuxetan) and Bexxar (tositumomab), both for non-Hodgkin lymphoma, are currently the only radioactive antibody-based drugs approved by the FDA. These drugs use MAbs that bring radioactive atoms directly to the cancer cells.

Angiogenesis inhibitors work by preventing angiogenesis, or the formation of new blood vessels in the tumor. This strategy shuts down a tumor’s blood supply to shrink the tumor, because tumors, like normal tissue, need nutrients and oxygen from blood to survive. Most antiangiogenic drugs target either the vascular endothelial cell growth factor (VEGF)—a protein secreted by certain tumors to promote the growth of new blood vessels—or the VEGF receptor on blood vessel cells. Avastin (bevacizumab) was the first successful drug to attack cancer in this way.

Avastin is a MAb that attaches to VEGF and prevents it from activating the VEGF receptor. Avastin is approved in combination with chemotherapy for colorectal cancer, non-small cell lung cancer, and breast cancer, and has shown benefit with chemotherapy in clinical studies for a variety of other cancers.

Antiangiogenic drugs that are not monoclonal antibodies include Revlimid (lenalidomide) and Thalomid (thalidomide), both approved for multiple myeloma, Sutent (sunitinib) for kidney cancer and gastrointestinal stromal tumors (GIST), and Nexavar (sorafenib) for kidney and liver cancers.

View Illustration: Antiangiogenesis: Starving the Tumor

Tyrosine kinase inhibitors are a significant advancement in targeted therapy. The drug Gleevec (imatinib) has changed the way doctors treat people with chronic myeloid leukemia (CML) and GIST. Almost all cases of CML have the Philadelphia chromosome, created when parts of chromosomes 9 and 22 break off and switch places. This produces an abnormal protein called bcr-abl, which is in a class of enzymes called tyrosine kinases.

Gleevec works by inhibiting bcr-abl, and almost all patients respond to this oral drug. Side effects are fewer than with traditional chemotherapy or interferon. Although Gleevec is highly effective against CML, some leukemias do not respond to the drug. Two new drugs, Sprycel (dasatinib) and Tasisna (nilotinib), are now approved for Gleevec-resistant CML.

Tarceva (erlotinib) is a kinase inhibitor approved for non-small cell lung cancer and pancreatic cancer. It blocks the overexpression of the epidermal growth factor receptor, or EGFR. Approved for advanced Herceptin-refractory breast cancer in 2007, Tykerb (lapatinib) inhibits both EGFR and HER2.

Proteasome inhibitors such as Velcade (bortezomib), which treats multiple myeloma and mantle cell lymphoma, block multi-enzyme complexes called proteasomes that break down proteins involved in regulating cell processes relevant to cancer. Inhibiting proteasome function increases levels of these regulatory proteins and helps restore some control over abnormal growth, survival, and spread of cancer cells.

mTOR inhibitors, a new class of targeted therapy, block the mammalian target of rapamycin (mTOR), a key protein in cells that regulates cell growth and survival. mTOR inhibitors block the translation of genes that regulate the cell cycle and reduce levels of certain cell growth factors involved in the development of new blood vessels, such as VEGF.

The only approved mTOR inhibitor is Torisel (temsirolimus), which was approved for kidney cancer in 2007. At press time, the FDA was reviewing another mTOR inhibitor, called everolimus, for approval in kidney cancer.

Immunotherapy uses the body's immune system to stimulate the production of T cells, specialized immune cells that recognize and kill cancer cells. Naturally occurring substances in the body called cytokines have been found to increase T-cell activity and signal the body to produce more T cells. Some cytokines, such as interleukins and interferons, can be produced in the laboratory for treating kidney cancer, melanoma, and bladder cancer.

Therapeutic vaccines represent an investigational form of immunotherapy. The theory behind vaccines is that by programming the body's immune system (both antibodies and T cells) to recognize and attack cancer cells, it will spare the normal tissue and destroy the cancer. So far, no vaccine has been approved to treat cancer, but many vaccine clinical trials are ongoing.

The basic principles of cancer therapy are straightforward—remove as much of the cancer as possible with surgery and/or radiation followed by drugs to affect the inner workings of cancer cells while leaving normal cells unharmed. But as simple as these principles are, the required expertise comes from different disciplines, including pathology, surgery, radiation, and medical oncology.

Multidisciplinary communication and coordination of care are becoming the norm, from large academic medical centers to community practices across the country. Colleagues from various specialties are now coming together to share their talents and experience to compose a tailored, state-of-the-art plan aimed at the best possible outcome for each patient.