

## FEATURE STORY

# About Cancer: Cancer Therapies

*An easy-to-understand review of common 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 keep it from coming back. This overview covers the types of treatment you may receive, including some new ones that have become available in the past few years.

## Surgery

If the cancer has not spread, surgery is often done to remove tumors and may require complete removal of the affected organ. Less invasive and less extensive methods are available in some cases. For example, laparoscopic surgery is less invasive because smaller incisions are needed. Lumpectomy is less extensive surgery for breast cancer than mastectomy because only the tumor tissue and a margin of surrounding healthy tissue is removed, not 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 body to remove the tumor. Disease-free survival and recurrence rates for many types of cancer seem to be about the same when laparoscopic surgery is compared with traditional open surgery. The main benefits are faster recovery time, shorter hospital stay, and less risk of complications.

**Robotic surgery**, a newer 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 (surgery to remove the prostate gland), 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 surgery. For this outpatient procedure, a thin needle-like probe is put into the tumor, and the tip is heated to kill 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 sometimes used alone to treat some cancers, such as prostate or cervical cancer, but is most often used in combination with other therapies. In addition, radiation can be used to improve the cure rate following surgery, to allow less extensive 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 put into or near the tumor. 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, still considered experimental, is increasingly being used for smaller lymph node-negative breast cancers and can be completed 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 in the brain. The treatment is usually done once, and the patient's skull must be held still inside 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 in the brain, while CyberKnife is typically employed for a variety of larger tumors.

**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. Experts say clinical research still needs to show that proton

beam therapy works better than standard radiation therapy at improving survival and quality of life for patients. Currently, only a handful of proton beam radiation centers are open in the United States, but more are scheduled to open soon.

## Chemotherapy

Several types of chemotherapy, each with its own mechanism of action and possible 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 lymphoma, chronic leukemias, and multiple myeloma, but are also effective in breast, ovarian, lung, and some gastrointestinal cancers. Some examples include cisplatin, carboplatin, Eloxatin (oxaliplatin), Cytosan (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. Examples include Gemzar (gemcitabine), 5-FU (fluorouracil),

Xeloda (capecitabine), Cytosar-U (cytarabine), Alimta (pemetrexed), and the recently approved Folutyn (pralatrexate). These agents are only effective in a specific cycle of cell growth and are used to treat leukemia, lymphoma, and cancers of the ovary, breast, gastrointestinal tract, and lung.

**Topoisomerase 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. Stem cells are the “parent cells” that develop into different types of blood cells, and some stem cells find their way into the bloodstream. Today, these stem cells can be “harvested” or removed from the blood using “apheresis” machines. They can also be collected 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 radiation and/or chemotherapy 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** (see illustration).

## 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 from a donor, they are usually infused in the patient soon after collection and may not need to be frozen. Over time, the cells find their way to the bone marrow, where they divide and mature into cells normally produced by healthy bone marrow. This process is 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 about 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 tumors. Hormonal therapy can be used alone or along with other treatments (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.

Over time this meant that the body’s immune system was primed to destroy the MABs before they could be helpful. Today, researchers have 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 has approved several MABs for the treatment of cancer, including Rituxan (rituximab) for non-Hodgkin lymphoma and some leukemias, Herceptin (trastuzumab) for HER2-positive breast cancer, Erbitux (cetuximab) for advanced colorectal and head and neck cancers, Vectibix (panitumumab) for advanced colorectal cancer, and Arzerra (ofatumumab) for chronic lymphocytic leukemia. 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, which shrinks the tumor, because tumors, like normal tissue, need nutrients and oxygen from blood to survive and grow. 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 advanced colorectal, non-small cell lung, breast, and kidney cancers, as well as glioblastoma. The drug has shown benefit with chemotherapy in clinical studies for a variety of other cancers, including gastric.

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

### View Illustration: Antiangiogenesis: Starving the Tumor

**Tyrosine kinase inhibitors** are a significant advancement in targeted therapy. Drugs in this class inhibit kinases with a wide variety of functions, including angiogenesis, growth factor receptors, and other aspects of cell signaling.

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 HER2-positive breast cancer, Tykerb (lapatinib) inhibits both EGFR and HER2.

**Proteasome inhibitors**, such as Velcade (bortezomib) that 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 FDA has so far approved two mTOR inhibitors, both for advanced kidney cancer. Torisel (temsirolimus) was approved in 2007, and Afinitor (everolimus) received approval in March 2009.

**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 and are used to treat 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 smaller 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.