Cancer Treatment

Targeted Therapy

Cancer treatment has evolved rapidly from surgery, radiation and traditional chemotherapy to targeted therapies that attack specific types of tumors and immunotherapies that help the immune system fight cancer.

Targeted therapies work against cancer with specific gene mutations or other unique characteristics that make cancer cells different from normal cells. Usually, this type of treatment interferes with processes needed for cancer to grow and spread.

Researchers have identified hundreds of so-called driver mutations that contribute to the development of cancer. Many of these either boost the activity of genes that cause uncontrolled cell growth (oncogenes) or turn off tumor suppressor genes. But despite this large number, a majority of people with cancer do not have driver mutations with known targeted therapies.

Some targeted therapies are monoclonal antibodies that are administered by IV infusion (usually indicated by the suffix -mab). Others are small molecules that can be taken as pills (indicated by the suffix -ib).

Unlike traditional cytotoxic chemotherapy, which kills both cancer cells and fast-growing normal cells throughout the body, targeted therapy acts directly and specifically against cancer. Therefore, targeted therapies are often better tolerated than chemotherapy because they don’t harm most types of healthy cells.

However, some targeted medications interfere with normal biological processes and can cause difficult side effects. For example, epidermal growth factor receptor (EGFR) inhibitors interfere with normal skin growth, which can lead to rashes and cracks in the skin.

Types of Targeted Therapy

Many targeted therapies interfere with cell communication or signaling pathways that regulate cell multiplication and death. Genetic mutations or gene fusions can cause receptors and other proteins involved in these processes to be overexpressed, or overactive, in cancer cells.

One widely used type of targeted therapy are kinase inhibitors, drugs that block the action of enzymes known as protein kinases. These enzymes carry out a chemical reaction called phosphorylation (adding phosphates to molecules), a necessary step in many biological processes. Phosphorylation can modify the function of proteins in a variety of ways, for example, increasing

or decreasing their activity.

Protein kinases modify proteins at specific locations, often at the amino acids tyrosine, serine or threonine. Kinases are involved in many signaling pathways that control cell proliferation. Overactive kinases can lead to the uncontrolled cell growth of cancer. Some targeted drugs inhibit a specific kinase, while others are multikinase inhibitors.

Gleevec (imatinib), one of the first targeted therapies, targets an abnormal tyrosine kinase seen in a certain type of leukemia. EGFR is a receptor tyrosine kinase associated with lung, colorectal and other types of cancer. Another tyrosine kinase, human epidermal growth factor receptor 2 (HER2), is overexpressed in about 20 percent of breast cancers, making them susceptible to HER2 blockers like Herceptin (trastuzumab). Up to half of melanomas have mutations affecting BRAF, a growth-promoting serine/threonine kinase, and can be treated with Zelboraf (vemurafenib).

Cyclin-dependent kinases (CDKs) bind to cyclins, proteins that regulate the cell division cycle. Some cancers have CDK mutations that trigger uncontrolled cell growth. New targeted therapies for breast cancer—Ibrance (palbociclib), Kisqali (ribociclib) and Verzenio (abemaciclib)—target both CDK4 and CDK6.

Normal cells have a variety of mechanisms to repair damage to their genetic material—,mechanisms that can malfunction in cancer cells. PARP inhibitors such as Lynparza (olaparib) work by blocking a protein that plays a role in DNA repair. Inhibiting PARP leads to more DNA breaks, which can halt cell division. People with BRCA mutations—which raise the risk of breast, ovarian and prostate cancer—do not make proteins that fix this kind of DNA damage, so BRCA-related cancers are particularly susceptible to these drugs.

Some of the first targeted cancer therapies were angiogenesis inhibitors, drugs that prevent the formation of new blood vessels needed to supply a growing tumor. Many tumors produce signals that stimulate angiogenesis, including vascular endothelial growth factor (VEGF). Some cancer drugs, such as Avastin (bevacizumab), bind to VEGF itself, while others, such as Nexavar (sorafenib), target its receptors.

Hormone or endocrine therapy, used to treat cancers that grow faster in the presence of sex hormones such as estrogen or testosterone, can be considered a type of targeted therapy. Hormone-blocking drugs, such as the estrogen receptor blocker tamoxifen and the androgen receptor inhibitor Erleada (apalutamide), deprive breast and prostate tumors of hormones that stimulate their growth.

Some targetable mutations occur at a low level in many different types of cancer. These include genetic mutations or gene fusions involving RET and TRK genes. These mutations occur in only around 1 percent of all cancers, but more often in certain rare cancers. The experimental drug larotrectinib targets cancer anywhere in the body with TRK fusions.

Making More Matches

Targeted therapies work very well for some people, but they are ineffective for others who may have the same type of cancer but a different genetic profile. And over time, cancer cells can become resistant to targeted therapies, meaning that they will stop working. The best outcomes may result from combination treatment using different targeted therapies together or combining targeted therapy with chemotherapy or immunotherapy.

The advent of targeted therapy has led to genetic testing to help guide treatment. These tests look for targetable, or actionable, mutations in a removed tumor or biopsy sample, enabling doctors to select which medications are most likely to work.

Many cancer-related mutations do not yet have matching medications. Researchers continue to look for additional targetable cancer characteristics and drugs that will work against them in the hope of making precision medicine available to more people. Clinical trials of new targeted therapies can be a good way to obtain promising experimental treatments.

The following resources offer more information about targeted therapy:

American Cancer Society

American Society of Clinical Oncology

National Cancer Institute

My Cancer Genome

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