Cancer Treatment

Immunotherapy

From surgery, radiation and chemotherapy to precision targeted therapies and immunotherapies that help the immune system fight cancer, cancer treatment has evolved rapidly in recent years. Most immunotherapies are biologic therapies, meaning they are produced by living organisms or are themselves “living drugs.”

Unlike traditional chemotherapy, which directly kills cancer cells, immunotherapy helps the immune system find and attack cancer cells, which can sometimes hide from immune cells or turn off natural immune responses. Some immunotherapies mark cancer cells and make them easier for the immune system to recognize. Others boost the activity of T cells or other immune cells.

T Cells and Cancer

T cells, a type of white blood cell produced in the bone marrow, are the main soldiers of the immune system. Killer T cells (also known as CD8 cells) patrol the body looking for invaders such as viruses and abnormal cells. But cancerous cells can sometimes hide from the immune system or turn off its defenses, allowing the cancer to grow out of control.

Immune Modulators

Cytokines are messenger proteins that immune cells use to communicate. Manufactured versions of natural cytokines that regulate immune response, such as interleukins and interferons, may be used to boost immune activity against cancer cells. Interleukin 2 (IL-2), which activates T cells, is approved to treat advanced melanoma and kidney cancer.

Immunomodulating drugs such as Thalomid (thalidomide), Pomalyst (pomalidomide) and Revlimid (lenalidomide) are thought to boost immune function by stimulating T-cell and natural killer cell activity. They are used to treat some blood cancers, especially multiple myeloma.

Checkpoint Blockers

Some cancers can disable the immune cells that fight them. Medications known as checkpoint inhibitors can restore the ability of T cells, the main soldiers of the immune system, to recognize and destroy cancer cells.

Most approved checkpoint inhibitors are monoclonal (genetically identical) antibodies that block the PD-1 receptor on T cells or PD-L1, its binding partner on cancer cells. PD-1 is an immune checkpoint that acts as a brake on T-cell activity. PD1 (which stands for “programmed death”) promotes T-cell suicide and down regulates, or turns off, immune responses. Normally, it prevents the immune system from attacking the body’s own tissues (known as autoimmunity).

Some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block PD-1 or PD-L1 release the brakes and restore T-cell activity against cancer cells. Keytruda (pembrolizumab), Opdivo (nivolumab) and Libtayo (cemiplimab) are PD-1 inhibitors. Bavencio (avelumab), Imfinzi (durvalumab) and Tecentriq (atezolizumab) are PD-L1 blockers. CTLA-4 is another immune checkpoint, which turns off immune responses by suppressing T-cell multiplication. Yervoy (ipilimumab) is an example of a CTLA-4 blocker.

Checkpoint blockers work best against so-called hot, or inflamed, tumors that have many mutations and attract T cells. Currently, PD-1 and PD-L1 drugs are approved for advanced melanoma, lymphoma, lung cancer, bladder cancer, head and neck cancer, and a few other types. Keytruda is approved for cancer anywhere in the body with a specific genetic feature known as high microsatellite instability. But checkpoint inhibitors do not work well against many other types of cancer, and even for responsive cancer types, they work for only a subset of patients.

Bispecific Antibodies

Bispecific antibodies have two binding sites. One site attaches to a T cell and the other to a cancer cell, bringing the T cell close enough to attack the tumor. Blincyto (blinatumomab)—which its maker calls a “bispecific T-cell engager”—is an example of this type of therapy.

Oncolytic Viruses

Oncolytic viruses are viruses that multiply in and kill cancer cells. These viruses, which can be naturally occurring or genetically engineered, can trigger immune responses, recruiting immune cells to attack and destroy infected cancer cells. Imlygic (talimogene laherparepvec), a genetically engineered herpesvirus, is an example of this type of therapy.

Cancer Vaccines

Therapeutic, or treatment, vaccines are designed to boost the immune system’s ability to recognize and attack cancer cells. These work differently than prophylactic, or preventive, vaccines such as those that protect against cancer-causing hepatitis B virus and human papillomavirus.

If checkpoint blockers work by taking the brakes off T cells, therapeutic vaccines are more like stepping on the accelerator. Therapeutic cancer vaccines generally work by training immune cells

to recognize antigens, or markers expressed on tumors (sometimes called neoantigens).

One approach uses killed cancer cells or antigens commonly found on a particular tumor type to encourage the immune system to produce antibodies against the tumor. These antigens are often administered with adjuvants, substances that boost immune response. In another approach, scientists create personalized vaccines that work against the specific set of neoantigens expressed on an individual tumor.

The Provenge (sipuleucel-T) prostate cancer vaccine works by removing a sample of dendritic cells—a type of immune cell that presents antigens to T cells—exposing them to a common prostate tumor antigen in a lab and then returning them to the patient. An experimental breast cancer vaccine takes a similar approach using the HER2 protein expressed by some breast tumors.

Cell Therapies

Some types of immunotherapy, known as adoptive cell transfer, involve administration of immune cells. An autologous transfer involves removing a sample of T cells from a patient using a process called apheresis, modifying them in a lab and returning them to the same individual. An allogeneic transfer uses immune cells from someone else, for example a bone marrow stem cell transplant from a donor. In some cases, the patient's diseased or ineffective immune cells are killed off with strong chemotherapy first to make room for the new ones.

One experimental approach involves removing part of a tumor and collecting the immune cells inside it, such as T cells and natural killer cells. These naturally occurring tumor-infiltrating lymphocytes (TILs), which are able to recognize the cancer, are multiplied in a lab and returned to the patient in larger numbers.

Another method uses a harmless virus to insert genes into a patient's T cells to make them express naturally occurring T-cell receptors (TCRs) that can recognize antigens inside cancer cells.

CAR-T

Chimeric antigen receptor T-cell therapy, or CAR-T, is a type of cell therapy in which a patient's T cells are genetically reprogrammed using artificial receptors engineered in a lab. These synthetic receptors bind to cancer cells more easily than natural TCRs.

One type of CAR-T uses gene therapy to produce T cells that bind to the CD19 protein on B cells, which grow out of control in some types of leukemia and lymphoma. Studies have shown that a single dose can sometimes produce a complete response (no remaining cancer) that lasts for years.

The first approved CAR-T therapies, Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), use this approach. A patient's T cells are collected, frozen and sent to a manufacturing facility, where they are genetically modified and multiplied in an incubator to create a customized "living drug" for each individual. The process, from T-cell extraction to reinfusion of the modified cells, usually takes around two weeks.

Researchers are working on other types of CAR-T that target different tumor antigens. Some researchers are trying to create "off-the-shelf" T-cell therapies that won't require harvesting and modifying each patient's own cells.

Immunotherapy Side Effects

Immunotherapy may be better tolerated than traditional chemotherapy or radiation therapy, which kill not only cancer cells but also rapidly dividing healthy cells throughout the body, including those in the gut, hair follicles and bone marrow.

But immune-based therapy can cause its own side effects. Boosting or taking the brakes off the immune system can lead to excessive immune responses that harm healthy tissues, with symptoms ranging from fever and flu-like symptoms to organ failure and death.

Checkpoint inhibitors work by restoring immune responses against cancer cells, but they can also activate the immune system more broadly. These drugs can cause excessive inflammation of almost any organ, including the lungs, intestines, liver, kidneys and hormone-producing glands.

CAR-T therapy can produce potentially fatal immune reactions. Unleashing genetically modified T cells can trigger cytokine release syndrome (CRS), also known as a cytokine storm. Severe CAR-T side effects may include low blood pressure, brain swelling and organ failure. Symptoms of brain inflammation can include confusion, memory problems and seizures. CAR-T therapy can also kill off too many healthy antibody-producing B cells, making a patient more prone to infections.

Some participants in clinical trials of CAR-T therapies have died due to CRS and brain swelling, but doctors are learning how to manage these side effects. For example, steroids or the immune-suppressing medication Actemra (tocilizumab), usually prescribed for rheumatoid arthritis, can help calm overactive immune responses.

The Future of Immunotherapy

Immunotherapy has seen impressive advances in recent years, producing long-term remission—and potentially a cure—for some people. But current approaches only work only for minority of patients, and it's hard to tell in advance who will respond.

What's more, some types of cancer are more susceptible than others to immunotherapy. So-called "hot" or inflamed tumors with many mutations respond better to checkpoint inhibitors than "cold" tumors that don't attract immune cells. Current CAR-T therapies work well against blood cancers but not against solid tumors. Some of the most common cancers (such as breast and prostate

cancer) and hard-to-treat cancers (like pancreatic cancer) usually do not respond to existing immunotherapies.

Researchers are looking for biomarkers that can help predict who will benefit and ways to make more types of tumors susceptible to immune-based treatment, as well as exploring entirely new approaches. The best outcomes may come from combining different approaches. Researchers have seen promising results from combining checkpoint inhibitors with one another or with other types of immunotherapy. Recent research suggests concurrent chemotherapy or radiation may make tumors more susceptible to checkpoint inhibitors. Hundreds of immunotherapy clinical trials are now enrolling participants, and this can be a good way to get access to promising experimental treatments.

Click here for a list of approved immunotherapy medications to treat cancer.

For more information on cancer immunotherapy, see:

American Cancer Society

American Society of Clinical Oncology

National Cancer Institute: Immunotherapy

National Cancer Institute: Cancer Vaccines

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