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Introduction

Surgery, chemotherapy, and radiation therapy have been the foundation of cancer treatment. Advances in the field of immunology (a branch of science that studies all aspects of the immune system) have led to a greater understanding of the ways in which the body's own defenses can be used to improve outcomes and lessen some of the toxic side effects of treatment for patients with blood cancers. Cancer researchers are now studying how harnessing the immune system can help destroy cancer cells.

The immune system is the body's defense against infection and cancer. It is made up of billions of cells that are divided into several different types. Lymphocytes, one type of white blood cell, comprise a major portion of the immune system. There are three types of lymphocytes: B lymphocytes (B cells), T lymphocytes (T cells) and natural killer (NK) cells. B cells make antibodies to fight infection; T cells and NK cells directly kill infected or cancerous cells and also talk to other cells of the immune system using chemicals known as "cytokines."

B cell lymphomas and leukemias arise when normal B cells mutate (change) and become cancerous. These cancerous B cells then multiply and crowd out normal B cells.

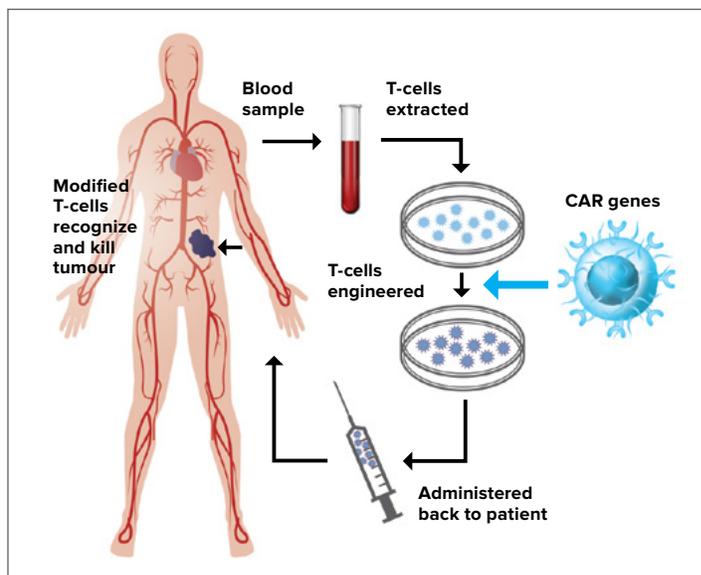
Immunotherapy improves the body's ability to detect and kill cancer cells. This approach to treatment is based on the concept that immune cells or antibodies can recognize and kill cancer cells. The immune cells or antibodies can be produced in the laboratory or in a drug manufacturing company under tightly controlled and regulated conditions, then given to patients to treat cancer. Several types of immunotherapy are either approved for use or are under study in clinical trials to determine their effectiveness in treating various types of cancer.

One type of immunotherapy involves engineering patients' own T cells to recognize and attack cancer cells. The receptor that is made on the T cells is called a "chimeric antigen receptor (CAR)." This treatment is known as "CAR T-cell therapy."

In CAR T-cell therapy, blood is taken from a patient and sent to a lab where the T cells are separated. These T cells are then modified to express a specific receptor—one that will allow the engineered T cell to find and kill the cancer cell. These engineered T cells are then multiplied in the lab and eventually given back to the patient through an intravenous infusion.

The most frequently targeted antigen (any substance that causes the immune system to produce antibodies against it) in CAR T-cell clinical trials for leukemia and lymphoma is called "cluster of differentiation (CD) 19." CAR T-cell trials targeting other antigens (BCMA, CD22, CD123, ROR-1, NKG2D ligands) are also under way. CD19 is expressed on the surface of nearly all healthy and cancerous B cells, including lymphoma and leukemia B cells. Because CD19 is not expressed on any healthy cells, other than B cells, it is an ideal target for CAR T-cell immunotherapy.

Chimeric Antigen Receptor T-Cell Therapy: How it Works



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T cells are collected from a patient. T cells are collected via apheresis, a process that withdraws blood from the body and removes one or more blood components (such as plasma, platelets or white blood cells). The remaining blood is then returned back into the body.

T cells are reengineered in a laboratory. The T cells are sent to a laboratory or a drug manufacturing facility where they are genetically engineered to produce chimeric antigen receptors (CARs) on their surface.

After this reengineering, the T cells are known as “chimeric antigen receptor (CAR) T cells.” CARs are proteins that allow the T cells to recognize an antigen on targeted tumor cells.

The reengineered CAR T cells are then multiplied.

The number of the patient’s genetically modified T cells is “expanded” by growing cells in the laboratory until there are many millions of them. These CAR T cells are frozen and, when there are enough of them, they are sent to the hospital or center where the patient is being treated.

At the hospital or treatment center, the CAR T cells are then infused into the patient. Many patients are given a brief course of one or more chemotherapy agents before they receive the infusion of CAR T cells. CAR T cells that have been returned to the patient’s bloodstream multiply in number. These are the “attacker” cells that will recognize, and kill, cancerous cells that have the targeted antigen on their surface.

The CAR T cells help guard against recurrence. CAR T cells may remain in the body long after the infusion has been completed. They guard against cancer recurrence, so the therapy frequently results in long-term remissions.

At this time, CAR T-cell therapy is only available to patients who are participating in a clinical trial. Trial protocols vary. Depending on the clinical trial, care may be provided in either a hospital setting or a treatment center. Patients may have to stay at the treatment facility, or they may need to plan to stay close by before, during or following treatment. Some trial protocols require patients to confirm the availability of a caregiver before they can enroll in the trial.

Possible Side Effects of CAR T-Cell Therapy

Cytokine-Release Syndrome (CRS).

A serious toxicity associated with CAR T-cell therapy is cytokine-release syndrome (CRS). CRS is the result of T-cell activation, so its presence actually indicates a positive response to therapy. Reinfused CAR T cells encountering their targets are rapidly activated, and cytokines (chemical messengers that help the T cells perform their duties) are released. The symptoms that some people experience with viral infections, such as the flu, are examples of a mild form of cytokine release. With CAR T-cell therapy, large amounts of cytokines are produced by the activated immune system. CRS in this setting may cause high fevers, low blood pressure or poor lung oxygenation (requiring administration of supplemental oxygen as a temporary measure). Some patients experience delirium, confusion and seizure while undergoing treatment. The onset of these symptoms is typically within the first week of treatment. The causes of CRS symptoms are not fully understood. One potential explanation is CAR T-cells secrete cytokines. These symptoms, however, are reversible.

In one small study of 40 patients, a little over half of them experienced CRS. CRS was grade 1 (mild) in 10 percent, grade 2 (moderate) in 17 percent, grade 3 (more severe) in 15 percent and grade 4 (life threatening) in 15 percent. Grade 1 CRS was mild and treated, for example, with medications that reduce fevers; grade 4 was life threatening at times, requiring assisted ventilation.

Patients with the most extensive disease prior to receiving CAR T cells are more likely to experience the more severe cases of CRS. Researchers discovered that patients with the most severe reactions expressed high levels of interleukin (IL)-6, a cytokine that is secreted by T cells in response to inflammation. Doctors have developed treatment plans to manage these more severe cases. Immune system suppressing medications such as corticosteroids are sometimes used. Other methods of decreasing the frequency of severe CRS are being explored including multiple-dose CAR T-cell therapy and decreasing the burden of disease prior to CAR T-cell infusion.

B-Cell Aplasia. CAR T-cell therapy targeting antigens found on the surface of B cells not only destroys cancerous B cells but also normal B cells. Therefore, B cell aplasia (low numbers of B cells or absent B cells) is an expected side effect. This absence of B cells results in less ability to make the antibodies that protect against infection. Intravenous immunoglobulin replacement is used to prevent infection. It is not known how long the decreased number of B cells persists however, no long-term side effects have been noted.

Tumor Lysis Syndrome (TLS). Another known side effect of CAR T-cell therapy is tumor lysis syndrome, a group of metabolic complications that can occur due to the breakdown of dying cells—usually at the onset of toxic cancer treatments. However, TLS can occur one month or more after CAR T-cell therapy. TLS can be a life-threatening complication of any treatment that causes breakdown of cancer cells, including CAR T cells. The complication has been managed by standard supportive therapy.

Results, Limitations, and the Future of CAR T-Cell Therapy

Early results from CAR T-cell trials have generated impressive results and considerable promise in patients with blood cancers. CAR T-cell therapy may represent options for acute lymphoblastic leukemia (ALL) patients who have relapsed after intensive chemotherapy or a stem cell transplant. In some studies, up to 90 percent of children and adults with ALL who had either relapsed multiple times, or failed to respond to standard therapies, achieved remission after receiving CAR T-cell therapy. Studies of CAR T-cell therapy in other blood cancers, including chronic lymphocytic leukemia (CLL), some types of non-Hodgkin lymphoma (NHL) including diffuse large B cell lymphoma (DLBCL) and follicular lymphoma, as well as multiple myeloma, are also very promising.

While data is fast emerging as to the early responses to CAR T-cell therapy, most of the patients participating in these clinical trials have only been followed for a relatively short period of time. Following these trial participants over the long term will provide information as to the length of their responses. It is important for more pediatric and adult patients to be enrolled in clinical trials. Larger study samples, looked at over more extended periods, will help researchers further understand the impact of this type of therapy, ways to reduce its toxicity and also improve toxicity management.

Researchers are in the relatively early stages of studying this treatment modality. Studies are under way to look at ways to improve the production of CAR T-cells; to identify additional targets and receptors and to decrease the side effects of CAR T-cell therapy.

We're Here to Help

LLSC offers free information and support for patients and families touched by blood cancers.

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