LEUKEMIA & LYMPHOMA SOCIETY®
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Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts

No. 27 in a series providing the latest information for patients, caregivers and healthcare professionals.

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Introduction

Historically, surgery, chemotherapy, and radiation therapy have been the foundation of cancer treatment. Spanning the last several decades, however, 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 toxic side effects of treatment for patients with blood cancers. In numerous studies, cancer researchers have focused on harnessing the immune system to 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, a subtype 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 lymphocytes make antibodies to fight infection; T lymphocytes and NK cells directly kill infected or cancerous cells and also talk to other cells of the immune system using chemicals known as "cytokines."

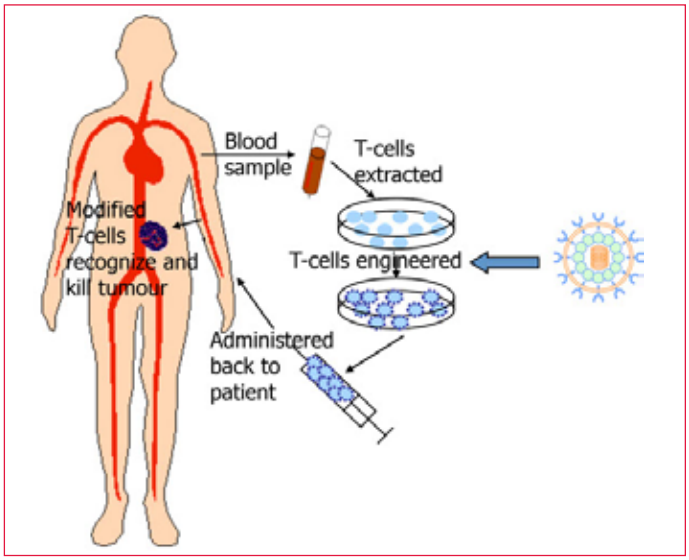
It is called B cell leukemia or lymphoma when the body's normal B cells become cancerous. These cancerous B cells are able to grow in the body by developing ways of making it hard for T cells to attack them successfully.

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 conditions regulated by the US Food and Drug Administration (FDA) and 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 immune cells first to recognize and then attack cancerous tumors. This approach, called "adoptive cell transfer (ACT)," has shown very promising results in patients with blood cancers. A patient's T cells are harvested using a large-volume blood draw and then modified so that they are better able to identify and attack the patient's cancer. The T cells are genetically engineered to produce receptors on their surface called "chimeric antigen receptors (CARs)." These receptors will recognize and bind to a specific target found on the cancerous cells. This is called "CAR T-cell therapy."

Clinical trials of CAR T-cell therapy in patients with leukemia and lymphoma have used T cells engineered to target the cluster of differentiation (CD) 19 and CD20 antigens. CD19 is expressed on the surface of nearly all healthy and cancerous B cells, including lymphoma and leukemia B cells. CD19 is not expressed on any healthy cells besides B cells. Therefore, it is an ideal target for CAR-modified T-cell immunotherapy. Additional B-cell-specific surface molecules, such as CD22, may hold similar promise and are also being investigated.

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 is similar in concept to a blood donation. However, with apheresis, usually larger volumes of blood are temporarily removed and then the remaining cells that are not needed for T-cell production are reinfused directly back into the patient.

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

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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 a specific protein (antigen) on targeted tumor cells.

These CAR T cells are then multiplied in the lab. The number of genetically modified T cells is "expanded" by growing them in the laboratory until about one hundred million of the modified T cells are available. Once enough of the cells are grown, they are sent back to the hospital or center where the patient is being treated.

These CAR T cells are then infused into the patient. When these "attacker" CAR T cells are returned to the patient's bloodstream, they multiply in number. At this point, they recognize and kill the cancerous cells that have the targeted antigen (any substance that causes the immune system to produce antibodies against it) on their surface.

The CAR T cells guard against recurrence. They may remain in the body long after the infusion and will continue to guard against cancer recurrence.

At present, CAR T-cell therapy is only available to patients through participation in a clinical trial. The amount of time that patients are required to be cared for in the hospital setting or treatment center, and the amount of time they need to stay close by before, during or following treatment, differs depending on the clinical trial. Some trial protocols may also require the patient to have a caregiver who can be available for a period of time. Patients may be asked to confirm the availability of a caregiver prior to enrollment in a trial.

Possible Side Effects of CAR T-Cell Therapy

Cytokine-Release Syndrome (CRS). The most common and potentially severe toxicity associated with CAR T-cell therapy is cytokine-release syndrome (CRS). When the reinfused CAR T cells encounter their target they are rapidly activated, resulting in the release of cytokines, chemical messengers that help the T cells perform their duties. The symptoms that some people experience with viral infections such as influenza represent a mild form of cytokine release. With cytokine-release syndrome after CAR T-cell therapy, large amounts of cytokines are produced by the activated immune system. CRS may cause high fevers, low blood pressure, poor lung oxygenation (temporarily requiring supplemental oxygen), and confusion or delirium.

For most patients, effects from CRS are mild enough that they can be managed with standard supportive therapies, including corticosteroids. In one trial, patients with the most extensive disease prior to receiving CAR T cells were 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. Two drugs that are approved to treat inflammatory conditions have been effective in its management: etanercept (Enbrel®) that blocks tumor necrosis factor (TNF) and tocilizumab (Actemra®) that blocks IL-6 activity.

B-Cell Aplasia. Low or absent numbers of normal B cells (B-cell aplasia) are expected as another toxicity of CAR T-cell therapies targeting B-cell malignancies, because CAR T cells kill normal B cells along with the cancerous B cells. While immunoglobulin replacements have been effective in preventing infectious complications associated with B-cell aplasia, longer follow up is needed to understand the effects of late toxicity of B-cell aplasia.

Tumor Lysis Syndrome (TLS). Another known side effect of CAR T-cell therapy is tumor lysis syndrome (TLS), a group of metabolic complications that can occur due to the breakdown of dying cells—usually at the onset of toxic cancer treatments. The potential severity of complications from TLS warrants preventive measures in patients who are at risk for this complication and requires immediate treatment in the event that TLS does occur.

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, including those with leukemia and lymphoma.

CAR T-cell therapy may represent options for acute lymphoblastic leukemia (ALL) patients who have relapsed after intensive chemotherapy or a stem cell transplant, whereas previous options for this subset of patients had been very limited. In fact, researchers reported that 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 CAR T-cell therapy. Another study showed similar results when treating children and young adults (aged 1-30 years) who had either relapsed or refractory ALL or non-Hodgkin lymphoma (NHL). Other CD19- and CD20-directed CAR T cells have also been shown to induce complete remissions in a significant group of patients with some types of NHL, including diffuse large B-cell NHL, as well as advanced heavily pretreated and high-risk chronic lymphocytic leukemia (CLL).

Relatively few patients have completed CAR T-cell therapy regimens, so most of these patients have only been followed for a relatively short period of time. It is crucial 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.

In addition, research groups are studying ways to improve the process by which CAR T cells are produced, to make a superior CAR T cell, including one with a better receptor that will identify new targets. The ability to reengineer T cells through the use of CARs has led to further efforts to extend this approach to other antigen targets and solid tumors. It will be challenging to identify these new, unique tumor antigens that can be targeted with selective CAR T-cell therapy.

Enrolling in a Trial

Talk with your doctor about whether participation in a CAR T-cell therapy clinical trial is an option for you. Obtaining another opinion from a hematologist-oncologist (a blood cancer specialist), may be helpful in finding additional clinical-trial information as well. When you discuss CAR T-cell therapy as a potential treatment option for you, it may be helpful to have

- A list of questions to ask concerning risks versus benefits of such a trial (visit www.LLS.org/whattoask for lists of suggested questions)
- A family member, friend, or another advocate with you for support and to take notes.

In addition to speaking with your doctor, LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists can search for clinical trials on behalf of patients, family members and healthcare professionals.

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the country and in Canada. To find the chapter nearest to you, visit our Web site at www.LLS.org/chapterfind or contact

The Leukemia & Lymphoma Society
1311 Mamaroneck Avenue, Suite 310
White Plains, NY 10605
Contact an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org.

LLS offers free information and services for patients and families touched by blood cancers. The following lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team members' knowledge and skills.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org
- Visit: www.LLS.org/informationspecialists.

Free Information Booklets. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please visit www.LLS.org/booklets.

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

Telephone/Web Education Programs. LLS offers free telephone/Web education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

Online Blood Cancer Discussion Boards and Chats. Online discussion boards and moderated online chats can provide support and help cancer patients to reach out to others in similar circumstances, and share information. For more information, please visit www.LLS.org/chat or www.LLS.org/discussionboard.

LLS Chapters. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support

program), in-person support groups, and other great resources.

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind.

Clinical Trials (Research Studies). New treatments for patients are ongoing. Patients can learn about clinical trials and how to access them. For more information, please

- Call: (800) 955-4572 to speak with our LLS Information Specialists who can help conduct clinical-trial searches
- Visit: www.LLS.org/clinicaltrials.

Advocacy. LLS enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy.

Another Resource

The National Cancer Institute (NCI)

www.cancer.gov
(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including CAR T-cell therapy. The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where patients can look for clinical trials.

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