LEUKEMIA & LYMPHOMA SOCIETY®

Chimeric Antigen Receptor (CAR) T-Cell Therapy

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

Highlights

- Autologous chimeric antigen receptor T-cell therapy (CAR T-cell therapy) uses a person's own immune system to identify and attack cancer cells.
- In CAR T-cell therapy, T cells are taken from a patient's blood and sent to a laboratory. There, technologies are used to genetically engineer T cells to express a particular chimeric antigen receptor, which allows the modified T cells to identify, attack and kill cancer cells. In the laboratory, the number of these engineered CAR T cells is multiplied, and these modified cells are frozen and sent to the patient's treatment center. There, they are infused into the patient's bloodstream, where they can seek out and kill cancer cells.
- The following CAR T-cell treatments have been approved by the US Food and Drug Administration (FDA): axicabtagene ciloleucel (Yescarta®), brexucabtagene autoleucel (Tecartus®), ciltacabtagene autoleucel (Carvykti™), idecabtagene vicleucel (Abecma®), lisocabtagene maraleucel (Breyanzi®) and tisagenlecleucel (Kymriah®). For prescribing information, see page 3.
- Serious side effects are linked with CAR T-cell therapy, some of which can be life-threatening. Active monitoring of a patient's condition after CAR T-cell infusion is critical to minimize the risk of serious side effects. Most side effects associated with CAR T-cell therapy can be managed with supportive care and medication.
- Factors associated with durable remission after CAR T-cell therapy include a deep initial response, lower extent of disease, absence of disease outside of the bone marrow and a higher level of circulating CAR T cells after infusion.
- Ongoing research efforts are focusing on improving the durability of response after CAR T cell therapy and the creation of novel CAR designs, including allogeneic or "off-the-shelf" CAR T cells.

Introduction

Surgery, chemotherapy and radiation are the traditional treatments for cancer. However, over the past three decades, a new method of treatment has been developed. This is called immunotherapy. Immunotherapies come in several forms, but the main idea is to use the immune system to identify and destroy cancer.

Immunology is the branch of science that studies all aspects of the body's immune system. Advances in this field have led to a greater understanding of the ways in which the body's own defenses can be harnessed to fight a variety of diseases, including blood cancers. Cancer researchers have been closely studying the immune system and learning how it can be used to destroy cancer cells. Chimeric antigen receptor (CAR) T-cell therapy is called "immunotherapy" because it uses a patient's own T cells to recognize and attack cancer cells.

This booklet provides a brief overview of the immune system and immunotherapy as well as information on how CAR T-cell therapy works and its role in the treatment of some blood cancers. It also includes important information on possible side effects.

The Natural Immune System and Immunotherapy

The immune system is the body's defense against infection and cancer. It is a network of cells and organs that defend the body from foreign substances. An antigen is a marker (usually a protein or sugar) that tells the immune system if something is harmful (foreign) or not. Antigens are found on viruses, bacteria, tumors and normal cells in the body. Antigens stimulate the immune system to make antibodies that target and destroy harmful (foreign) agents. This is known as the body's "immune response."

Lymphocytes are a type of white blood cell. Like other white blood cells, they help the body fight off infections. Lymphocytes are mainly found in the lymph nodes, spleen, bone marrow, thymus and some other parts of the lymphatic system. Some lymphocyte cells enter the bloodstream. There are three major types of lymphocytes: T lymphocytes (T cells), B lymphocytes (B cells) and natural killer (NK) cells. B lymphocytes make antibodies that recognize and target antigens. B lymphocytes are found in the bone marrow and other parts of the lymphatic system. T lymphocytes mature in the thymus and have several functions, including helping B lymphocytes make antibodies against invasive organisms and killing infected cells in the body. Natural killer cells can also attack cancer cells and eliminate viruses.

B-cell lymphomas and leukemias begin when normal B cells mutate (change) and become cancerous. These cancerous B cells multiply uncontrollably. B cells can also develop into plasma cells. When normal plasma cells mutate, they can become cancerous. That is how myeloma begins.

Immunotherapy improves the body's ability to detect and attack cancer cells. It is an active area of clinical research, and there are proven immunotherapy treatments for people with certain types of cancer. Many immunotherapies are either approved for use or are under study in clinical trials to determine their effectiveness in treating various types of cancer. In addition to CAR T-cell therapy, other types of immunotherapies include monoclonal antibody therapy, radioimmunotherapy, antibody drug conjugates and therapeutic cancer vaccines.

Visit www.LLS.org/booklets for the free LLS booklet *Immunotherapy* for more information about immunotherapy treatments.

Chimeric Antigen Receptor (CAR) T-Cell Therapy

Autologous CAR T-cell therapy involves genetically engineering a patient's own T cells to recognize and attack cancer cells. "Autologous" means the use of an individual's own cells or tissues in this therapy.

The most frequently targeted antigen in CAR T-cell immunotherapy for leukemia and lymphoma is called "cluster of differentiation 19 (CD19)." The CD19 antigen is present on the surface of nearly all cancerous B cells. It is also present on healthy (non-cancerous) B cells, but it is not found on other types of cells. Since the human body can tolerate prolonged periods of B-cell loss (depletion), CD19 is considered an ideal target antigen for CAR T-cell immunotherapy (see B-Cell Aplasia on page TK). Trials of treatments using CAR T cells that target other antigens expressed on various blood-related cancers are also under way (see **Table 1** on page 4). Since 2017, six CAR T-cell therapies have been approved by the US Food and Drug Administration (FDA). These are approved for the treatment of blood cancers, including some types of lymphoma, B-cell acute lymphocytic leukemia and multiple myeloma.

The Chimeric Antigen Receptor (CAR) T-Cell Process

T cells are collected from a patient. Using a procedure called "apheresis," blood is temporarily removed from the patient's veins and put through an apheresis machine that separates the blood into its four components: red blood cells, white blood cells, platelets and plasma. White blood cells are collected, and the T cells are removed. The remaining blood is infused back into the patient's body. See **Figure 1** on page 3.

T cells that have been genetically engineered in a laboratory can recognize antigens on the surface of tumor cells. The patient's T cells are sent to a laboratory or a drug manufacturing facility for genetic engineering. Deoxyribonucleic acid (DNA) is introduced into the cells to produce chimeric antigen receptors (CARs) on the surfaces of the cells. CARs are artificial receptors that allow the T cells to recognize antigens on targeted (cancer) cells. **These engineered T cells are known as "chimeric antigen receptor (CAR) T cells."**

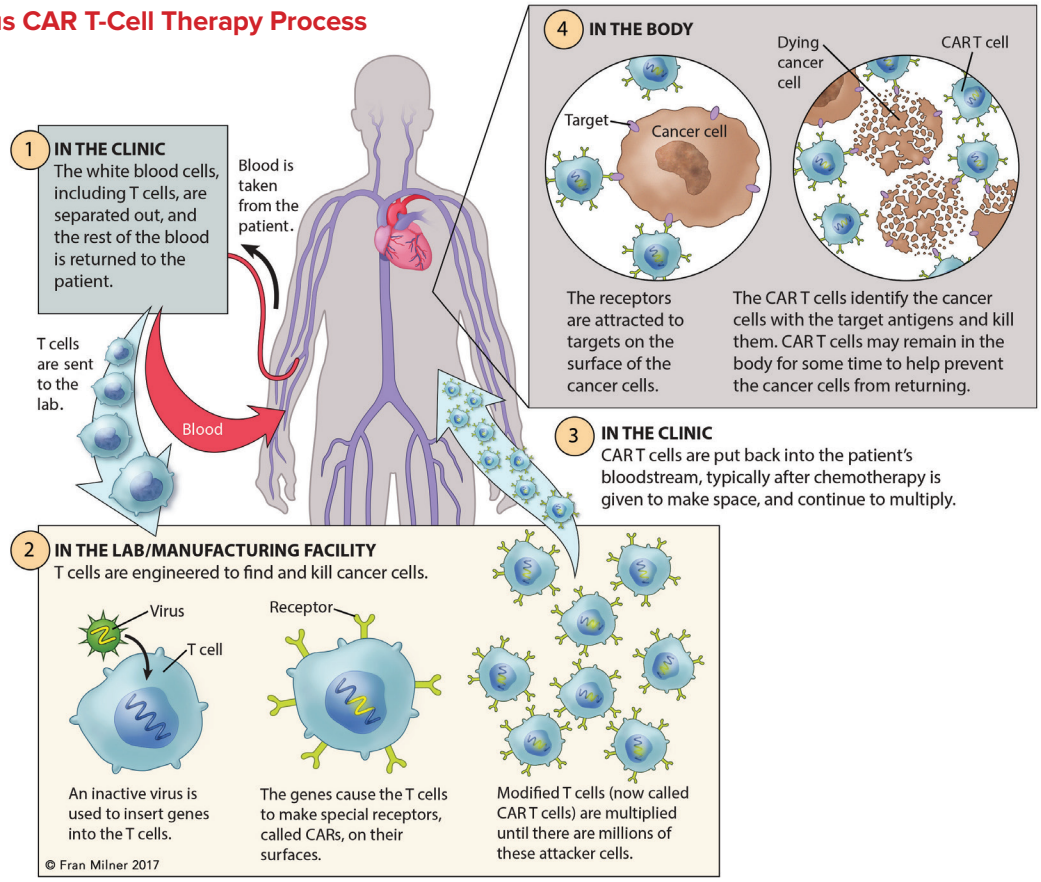
The number of engineered CAR T cells is then multiplied. The number of the patient's genetically modified T cells is "expanded" by growing them in the laboratory. When there are enough of them, the CAR T cells are frozen and sent to the hospital or treatment center where the patient is receiving care. The method used to collect cells and complete this "manufacturing process" takes from 3 to 4 weeks.

At the hospital or treatment center, the CAR T cells are thawed and then infused into the patient. Many patients are given a brief course of one or more chemotherapy agents to reduce the number of normal T cells in the body. This is called "lymphodepletion." This process is important because it "makes space" for the CAR T cells in the patient receiving the infusion. The genetically modified CAR T cells are then infused into the patient's bloodstream via an intravenous (IV) infusion or through an existing central line. The process usually takes less than 30 minutes. In the body, the CAR T cells seek out cancer cells that express the antigen that they have been trained to target. These "attacker" cells recognize and destroy cells that have the target antigen on their surfaces. When they encounter the antigen, the CAR T cells become activated. They then attack and kill the cancer cells. These T cells begin making copies of themselves and increase in number throughout the body.

The CAR T cells may help guard against recurrence. The CAR T cells may not only eradicate all the cancer cells in the body, but they may remain in the body for months after the infusion has been completed. This therapy has resulted in long-term remissions for some patients with certain types of blood cancer.

There are currently **six** approved CAR T-cell therapies. The package insert and/or the full prescribing information for each medication is available on the internet.

Figure 1. Autologous CAR T-Cell Therapy Process



Axicabtagene ciloleucel (Yescarta®) has been FDA approved since 2017 for the treatment of the following groups of patients:

- Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL).
- Adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

Axicabtagene ciloleucel is a CD19-directed genetically modified autologous T-cell immunotherapy. Axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

Brexucabtagene autoleucel (Tecartus®) has been FDA-approved since 2020 for the treatment of adult patients with these conditions:

- Relapsed or refractory mantle cell lymphoma (MCL)
- Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Tecartus is a CD19-directed genetically modified autologous T-cell immunotherapy.

Ciltacabtagene autoleucel (Carvykti™) has been FDA-approved since 2022 for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

Ciltacabtagene autoleucel is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy.

Idecabtagene vicleucel (Abecma®) has been FDA-approved since 2021 for the treatment of adult patients with relapsed or refractory multiple myeloma after two or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Idecabtagene vicleucel is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy.

Lisocabtagene maraleucel (Breyanzi®) has been FDA-approved since 2021. It is indicated for the treatment of:

- Adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:
  - refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
  - refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
  - relapsed or refractory disease after two or more lines of systemic therapy.
- Adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor.
- Adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy.
- Adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor.

Lisocabtagene maraleucel is a CD19-directed genetically modified autologous T-cell immunotherapy. Lisocabtagene maraleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

Tisagenlecleucel (Kymriah®) has been approved by the US Food and Drug Administration (FDA) since 2017 for the treatment of these groups of patients:

- Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (B-ALL) that is either refractory or in a second or later relapse.
- Adult patients with relapsed or refractory large B-cell lymphoma who have had two or more lines of systemic therapy. This group includes people with diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL).
- Adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

Tisagenlecleucel is a CD19-directed genetically modified autologous T-cell immunotherapy. Tisagenlecleucel is not indicated for the treatment of patients with primary central nervous system lymphoma. Patients treated with tisagenlecleucel who need to receive additional treatment after CAR T-cell therapy will be screened for HIV (human immunodeficiency virus). These patients may show a false-positive HIV test result due to the virus used to generate the CAR T cells. Patients are advised to talk with their healthcare team about their concerns. They should also ask questions.

Table 1 below lists some of the CAR T-cell therapy antigen targets that are approved for use by the FDA or that are under study in clinical trials for hematologic malignancies and their potential off-tumor targets.

Table 1. Select Antigens Being Targeted in CAR T-Cell Trials for Hematologic Malignancies and Potential Off-Tumor Targets

Antigen	Hematologic Malignancy	Potential Normal Tissue Targeted (Off-Tumor Target)
CD5	T-ALL, T-cell lymphoma	Normal T cells
CD7	T-ALL, T-cell lymphoma	Normal T cells
CD19	ALL, CLL, NHL	Normal B cells
CD20	ALL, CLL, NHL	Normal B cells
CD22	B cell leukemias; B-cell lymphomas	Normal B cells
Igκ	CLL, NHL, myeloma	Normal B cells
ROR1	CLL, NHL	Pancreas parathyroid, adipose (fat) tissue
CD30	NHL, HL	Resting CD8 T cells
CD33	AML	Multipotent myeloid precursors, unipotent colony-forming cells, and maturing granulocytes and monocytes
CLL-1	AML	Peripheral blood leukocytes and in the spleen
CD138	Myeloma	Precursor and plasma B cells, epithelia
CD123	AML	Bone marrow myeloid progenitors, B cells, mast cells, monocytes, macrophages, endothelial cells
BCMA	Myeloma	B cells

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCMA, B-cell maturation antigen (also known as "tumor necrosis factor receptor"); CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; CLL-1, C-type lectin-like molecule-1; HL, Hodgkin lymphoma; Igκ, immunoglobulin kappa light chain; NHL, non-Hodgkin lymphoma; T-ALL, T-cell acute lymphoblastic leukemia.

Source: Zhang X, Zhu L, Zhang H, Chen S, Xiao Y. CAR-T Cell Therapy in Hematological Malignancies: Current Opportunities and Challenges. *Front Immunol.* 2022;13:927153. Published 2022 Jun 10. doi:10.3389/fimmu.2022.927153

Clinical Trials. Chimeric antigen receptor T-cell therapy has shown varying degrees of efficacy in clinical trials for the treatment of leukemia, lymphoma and myeloma. Even though CAR T-cell therapy is FDA-approved for the treatment of some cancers, the use of this treatment is still being researched in clinical trials to determine if other diseases may respond to CAR T-cell therapy and improve outcomes. Trial protocols vary. Depending on the clinical trial, care may be provided in either a hospital or an outpatient treatment center staffed by healthcare professionals who have experience administering cellular immunotherapy.

Patients may have to stay at the treatment facility, or they may need to plan to stay nearby before, during or following treatment. Some trial protocols require patients to confirm the availability of a caregiver before they can enroll in the trial. If there is concern about finding a caregiver, your healthcare team can help identify appropriate caregivers from their support system.

The Relationship between Hematopoietic Stem Cell Transplantation and CAR T-Cell Therapy. Allogeneic and autologous stem cell transplantation and CAR T cell therapy are treatment approaches that have the potential to induce long-term deep remissions for many blood cancer patients. Each presents their own set of advantages and potential disadvantages.

Autologous transplantation allows for stem cell rescue following the administration of high-dose chemotherapy to people with multiple myeloma, relapsed lymphomas, and some other conditions. In contrast, allogeneic stem cell transplantation not only uses high-dose chemotherapy, but it also employs the graft-versus-tumor effect that results from the transfer of donor immune cells. This approach has been successful in treating acute lymphoblastic leukemia, some types of NHL and other blood cancers, such as AML and MDS. The development and success of CAR T-cell therapy in clinical studies has challenged the transplantation-based standard of care in relapsed and refractory B-cell NHL and multiple myeloma.

Recent and ongoing clinical trials have been examining the relationship between hematopoietic stem cell transplantation and CAR T-cell therapy. Whether these approaches complement or compete with one another depends on disease and patient features and requires an individualized approach by the treatment team.

Ongoing clinical trials are researching how CAR T-cell therapy can be used as one or more of these treatment options:

- A destination or “bridge” to allogeneic stem cell transplant to induce deep remission in patients and possibly increase the likelihood of successful transplantation, such as in patients with relapsed and refractory B-cell ALL.
- A potential treatment alternative to allogeneic stem cell transplantation in patients with refractory, active or progressive disease, such as relapsed and refractory multiple myeloma.
- A treatment approach for relapsed B-cell cancers after allogeneic stem cell transplantation failure, as in patients with relapsed B-cell ALL.

For more information, please see the LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Possible Side Effects of Chimeric Antigen Receptor (CAR) T-Cell Therapy

While many patients have reported only mild to moderate side effects with CAR T-cell therapy, this treatment is sometimes associated with serious side effects. It is important to speak with your doctor about potential side effects before starting any treatment.

Most side effects resulting from CAR T-cell therapy will either resolve on their own or can be managed with appropriate treatment. Some of the most common potential side effects of CAR T-cell therapy include cytokine release syndrome (CRS); neurologic toxicities (immune effector cell-associated neurotoxicity syndrome [ICANS]); tumor lysis syndrome; anaphylaxis; and (in cases of cluster of differentiation 19 (CD19)-targeting CAR), B-cell aplasia. All treatment centers certified to infuse CAR T cells employ evidence-based strategies to minimize and treat these side effects. Each of these side effects is discussed in detail in the following sections.

Cytokine Release Syndrome. This potentially serious side effect is frequently associated with CAR T-cell therapy. Cytokines (chemical messengers that help the T cells carry out their functions) are produced when the CAR T cells multiply and kill cancer cells. When the CAR T cells encounter their antigen targets, they are rapidly activated. At this point, numerous inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNFα) and interferon gamma (IFNγ), are released. The large amounts of cytokines produced and then released by the activated immune system cause a collection of mild to potentially life-threatening signs and symptoms. This is known as “cytokine release syndrome (CRS).”

Common signs and symptoms of CRS can include:

- Fever
- Fatigue
- Headache
- Hypotension (low blood pressure)
- Hypoxia (lack of oxygen reaching the tissue)
- Tachycardia (abnormally rapid heart rate)
- Chills

These are some of the more serious symptoms of CRS:

- Capillary leak (fluid and proteins leaking out of tiny blood vessels and flowing into surrounding tissues, resulting in dangerously low blood pressure and difficulty breathing)
- Cardiac arrest (the heart stopping)
- Cardiac arrhythmia (abnormal heartbeat)
- Cardiac failure (heart failure)
- Encephalopathy (damage or disease that alters brain function or structure)
- Hemophagocytic lymphohistiocytosis (HLH) (life-threatening immune system condition when T and natural killer (NK) cells become overactive causing too much inflammation)/macrophage activation syndrome (MAS) (an uncontrolled immune system working overtime, leading to inflammation)
- Renal insufficiency (poor kidney function)
- Poor lung oxygenation
- Multiple organ failure

Healthcare workers caring for patients receiving CAR T-cell therapies have been trained to recognize and treat signs and symptoms of CRS.

A patient with severe CRS may require intensive care treatment. Although most signs and symptoms are reversible, the potentially life-threatening risk of this side effect of CAR T-cell therapy should not be underestimated. Deaths have been reported both in CAR T-cell therapy trials and after infusion of FDA-approved CAR T cells.

Doctors use a grading system to assign CRS a level from 1 (mildest) to 4 (most severe). This grade helps the treatment team make informed decisions about your treatment. Depending on the severity of CRS, patients may require only supportive care with fever-reducing medications and intravenous (IV) fluids. This will depend on decisions made by your doctors and will depend on how you respond to treatment. In some cases, you may require rapid intervention with immunosuppressive anti-cytokine-directed therapy and/or corticosteroids to reduce the symptoms of CRS. Researchers have discovered that patients with the most severe reactions expressed high levels of IL-6 (and other cytokines). These are secreted by T cells and other immune cells that are activated in response to inflammation. The challenge for researchers has been to find an appropriate therapy that eases the symptoms of uncontrolled inflammation without diminishing the antitumor effectiveness of the engineered T cells. Recent research has shown that the effects of CRS can be lessened by the infusion of the monoclonal antibody **tocilizumab (Actemra®)**, which blocks the IL-6 receptor and reduces inflammation without compromising the effectiveness of FDA-approved CAR T cells. Tocilizumab is approved by the FDA for the treatment of adults and pediatric patients 2 years of age and older who have either CAR T-cell-induced, severe or life-threatening CRS.

If signs and/or symptoms of severe CRS either do not improve with tocilizumab alone, or if they are getting worse, IV corticosteroids such as dexamethasone and methylprednisolone are typically used together with tocilizumab to reverse CRS. It is not known whether high doses of corticosteroids affect the ability of CAR T cells to destroy the cancer cells, but patients who have received corticosteroids have achieved long-lasting remissions. When CRS is life-threatening, corticosteroids may be the only way to stop symptoms from getting worse.

Other methods that aim to reduce the risk of developing severe CRS are being explored in clinical trials. They include the following:

- Using multiple low-dose CAR T-cell therapy infusions (instead of one single higher-dose infusion)
- Treating patients earlier in the course of their disease
- Decreasing the burden of disease prior to CAR T-cell infusion through “bridging” therapies such as chemotherapy, targeted therapy or radiation therapy

Depending on the patient and the CAR T cells, CRS may occur within 1 to 21 days of CAR T-cell infusion. The duration of CRS is variable and depends on a number of factors, including the type of intervention used to manage it.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). The connection between CRS and neurologic adverse events is not completely understood. The frequency, severity and nature of neurological toxicity is different among CAR T-cell products. This could be due to either differences in the products, the relatively small number of patients studied or both. The effects of ICANS have been observed in patients undergoing CAR T-cell

treatment of acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), B-cell non-Hodgkin lymphoma (NHL) and multiple myeloma (MM). Common signs and symptoms of ICANS include language impairment (aphasia), confusion, delirium, involuntary muscle twitching, hallucinations or unresponsiveness. Seizures have also been reported. The underlying cause of ICANS is unclear. It is not known whether the presence of CAR T cells in the central nervous system is related to either the occurrence or the severity of neurotoxicity. The cause of neurotoxicity is the subject of intense investigation by researchers.

Neurotoxicity is reversible in most cases, and signs and/or symptoms usually resolve over several days without intervention or apparent long-term effects. However, neurologic complications of CAR T-cell therapy can be life-threatening. Harmful neurological events have been reported. Cerebral edema (swelling in the brain) is the most common; however, a number of other neurological complications may occur, as well. Additionally, there have been fatalities. Some symptoms of neurologic toxicity can be treated with anti-epileptic medication and/or corticosteroids. Some patients may receive prophylactic (preventative, before CAR T-cell therapy) anti-epileptic medications, such as **levetiracetam (Keppra®, Keppra® XR,** and **Spritam®).** Sometimes a lumbar puncture (a procedure typically used to remove a sample of spinal fluid for testing) may be used to relieve pressure from brain swelling caused by severe ICANS. CAR T-cell therapy is new, and much more research is needed to understand the mechanisms of action, management of symptoms, and risk factors associated with ICANS.

Signs and symptoms of ICANS can sometimes be subtle. As a result, patients are frequently asked to complete a series of assessments during their treatment to ensure that they do not have neurologic toxicities. This assessment may include asking patients to write a sentence, to report the date, or perform other simple tasks to demonstrate that they do not have any neurologic symptoms.

If patients with CRS and ICANS continue to worsen while being treated with tocilizumab and corticosteroids, siltuximab, another monoclonal antibody that binds to IL-6, may be used. A second alternative is Anakinra, which is a medication that blocks the IL-1 receptors and is used for the treatment of many inflammatory conditions. This drug has shown promising results in studies for the treatment of CRS and ICANS that do not respond to corticosteroids and tocilizumab.

Tumor Lysis Syndrome (TLS). This syndrome is another known side effect of CAR T-cell therapy. It is a group of metabolic complications that can occur due to the breakdown of dying cancer cells. It usually happens at the beginning of some types of cancer treatments. However, the onset of TLS can occur at any time, even a month or more after the initiation of CAR T-cell therapy. Tumor lysis syndrome can cause damage to organs, such as the kidneys, and it can be a life-threatening complication of any treatment that involves the breakdown of cancer cells. Tumor lysis syndrome is managed by standard supportive therapy, including hydration (water and fluids) and the medications **allopurinol (Zyloprim®, Aloprim®)** and **rasburicase (Elitek®). These two drugs** manage the levels of uric acid in the body.

Anaphylaxis (Life-Threatening Allergic Reaction). There is potential for a patient receiving CAR T-cell therapy to have an overwhelming immune response (an anaphylactic reaction) to the CAR (chimeric antigen receptor) itself. Signs and symptoms associated with anaphylaxis include hives, facial swelling, low blood pressure and respiratory distress. There have been reports of acute anaphylaxis with CAR T-cell infusion. Immediate treatment and thorough monitoring of this life-threatening side effect are critical for patients receiving CAR T-cell therapy.

B-Cell Aplasia. Chimeric antigen receptor T-cell therapy that targets antigens found on the surface of B cells destroys not only cancerous B cells but also normal B cells. Therefore, B-cell aplasia (a low number of healthy B cells or absent B cells) is an expected result of successful CD19-specific CAR T-cell treatment, and it has served as a useful indicator of ongoing CAR T-cell activity. This adverse effect also results in the body's reduced ability to make the antibodies that protect against infection. Intravenous or subcutaneous immunoglobulin replacement therapy may be given to prevent infection, especially in patients who experience recurrent or severe infections. B-cell depletion (loss of B cells) has been reported in nearly all patients treated with CD19-targeted CAR T cells. Depending on the CAR T-cell configuration, B-cell aplasia can last from months to years. Long-term follow-up analysis is needed to assess the late effects of B-cell aplasia.

Infection. In addition to low numbers of healthy B cells (aplasia), a number of patients (20% to 40%) who receive CAR T-cell therapy may have prolonged cytopenias. This is when a patient has a low number of white blood cells, red blood cells or platelets. Cytopenia can result

in serious bacterial, viral or fungal infections. Additionally, opportunistic infections (infections that occur due to a unique opportunity, such as a weakened immune system) can occur. The most common types of infections occur within the first three months following the CAR T-cell infusion are upper and lower respiratory tract infections.

As a precautionary measure, following CAR T-cell therapy, depending on the patient's blood cell count recovery, most patients will be maintained on prophylactic antimicrobial therapy (treatment designed to prevent an infection from occurring).

Immunizations

Since CAR T-cell therapy is a relatively new treatment, there is still much that needs to be learned about the use of vaccines. Experts believe that vaccination after CAR T-cell therapy is an important part of the long-term follow-up plan for patients.

In general, for patients who are in remission and do not require any additional chemotherapy or stem cell transplantation, vaccinations should be administered. Killed/inactivated vaccines should be considered six months after receiving the CAR T-cell therapy infusion, and live vaccines can be given one year following infusion.

Patients need to speak to their doctors and follow their doctors' recommended vaccination schedule. COVID-19 and flu vaccines are also recommended. For more information, patients should consult with their doctors.

Pediatric and Adolescent Chimeric Antigen Receptor (CAR) T-Cell Therapy

Tisagenlecleucel (Kymriah®) is approved by the FDA for treatment of pediatric and adolescent patients with B-cell precursor acute lymphoblastic leukemia (B-ALL). The FDA's decision was based on this drug's remarkable success in early clinical trials.

Disease distribution in this population and treatment regimens prior to CAR T-cell therapy will be different from those that exist for adults. These factors may be important to consider when assessing potential differences in response rates and the toxicity profile. It is important to discuss such issues with members of your healthcare team to learn how treatment of children with CAR T-cell therapy may differ from the treatment of adults.

For pediatric and young adult patients who qualify for a CAR T-cell therapy clinical trial, the process of enrolling in a trial is often much slower than it is for adults. This is due to the need to demonstrate the drug's safety and tolerability in adults before it can be studied in younger patients.

Financial Concerns

CAR T-cell therapy is an expensive treatment that may not be fully covered by health insurance. Medicare covers CAR T-cell therapy for eligible patients, and Medicaid covers it as well (but only in certain states). Even when healthcare plans cover the treatment, patients may have significant out-of-pocket expenses for time off work, transportation, lodging costs, caregivers, meals and childcare.

Patients can speak to their healthcare team if they have any concerns about being able to afford CAR T-cell therapy. A member of the team may be able to provide information and suggest resources that can help. Health insurance plans may not cover all the costs associated with this care, but patients can ask for referrals to organizations that can help them find assistance.

You can contact an LLS Information Specialist at (800) 955-4572 for information about our Co-Pay Assistance Program and other financial assistance programs. For more information and resources to cope with the financial aspects of cancer care, see the free LLS booklet *Cancer and Your Finances*.

Follow-Up Care

Some patients will receive their CAR T-cell therapy in a different center from the place where they received their initial cancer treatment. If this is the case, it is important for patients to have their CAR T-cell therapy oncologist connect with, and stay in touch with, their primary hematologist/oncologist to continue proper management of care. Follow-up appointments for CAR T-cell therapy will include laboratory work, supportive care and possibly imaging tests (such as x-rays, computerized tomography (CT) and magnetic resonance imaging (MRI) scans, etc). A patient's local hematologist/oncologist should continue cancer checkups. Patients are advised to have their caregivers accompany them to these appointments, since these are the people who have been with them throughout the CAR T-cell treatment process, and they may be the first to notice any changes or side effects the patient may be experiencing.

Most patients receiving CAR T-cell treatment have been followed for a relatively short time; however, data providing information about responses to therapy (including duration of response) is developing at a rapid pace. Researchers

will be able to better predict the duration of these responses after patients have been followed over longer terms. Patients who have had CAR T-cell treatment face long-term and late effects that are similar to those of patients who have received traditional types of therapy for their cancer. It is especially important to follow up on potential fertility and endocrine late effects.

It is especially important for pediatric, young adult and adult patients to be enrolled in clinical trials. Larger study sizes, evaluated over more extended periods, will help researchers further understand the impact of this type of therapy. It will also help them improve treatments and learn how to better prevent and manage side effects.

Results, Limitations and the Future of Chimeric Antigen Receptor (CAR) T-Cell Therapy

Results and Long-Term Outcomes. Chimeric antigen receptor T-cell clinical trials have generated impressive results in the early outcomes of patients with blood cancers. With the FDA approval of **axicabtagene ciloleucel (Yescarta®), brexucabtagene autoleucel (Tecartus®), ciltacabtagene autoleucel (Carvykti™), idecabtagene vicleucel (Abecma®), lisocabtagene maraleucel (Breyanzi®),** and **tisagenlecleucel (Kymriah®),** CAR T-cell therapy represents a potential to treat certain leukemias, lymphomas and myeloma in patients whose disease has relapsed or is refractory to treatment.

In some studies, up to 90 percent of children and adults with B-ALL, whose disease had either relapsed multiple times or failed to respond to standard therapies, achieved remission after receiving CAR T-cell therapy. Even though some of these therapies have only been recently approved by the FDA, they have been studied for many years in clinical trials prior to their approval. Data from long-term outcome studies following CAR T-cell therapy indicates that CD19-targeted CAR T cells can induce prolonged remissions in patients with B cell malignancies, while remissions induced by BCMA-targeted CAR T cells are typically more short-lived. Additionally, certain patient and disease factors are associated with achieving durable remissions after CAR T-cell therapy. These are listed in the box in the column found at the right side of this page.

Limitations of CAR T-Cell Therapy. While CAR T-cell therapy has achieved great clinical results, there are some disadvantages to this type of therapy. The products are generated from a patient's autologous T cells, which requires extensive and costly collection and manufacturing efforts. The time between apheresis (when the patient's T cells are collected) to the infusion of the engineered CAR T cells back to the patient is called the "vein-to-vein" time. Currently, all FDA-approved products require three to five weeks of manufacturing and quality assessment before the product is available to the patients. This delay can be problematic in some patients with certain diseases, such as acute leukemia, who may show disease progression before an autologous CAR T-cell treatment is ready for use.

Factors Associated with Durable Remissions After CAR T-cell Therapy

- **Depth of response**
  - Patients with deeper initial remissions are more likely to have long-term responses; however, disease relapse can occur even after deep MRD-negative remissions.
- **Type of Blood Cancer**
  - Patients with B cell lymphomas are less likely to have a complete response (CR) but are more likely to have a sustained remission once a CR has been reached.
  - Patients with B cell ALL or multiple myeloma are more likely to have a CR, although they are less likely to have a sustained remission.
- **Tumor burden/Extent of disease and location**
  - Patients with lower extent of disease or tumor burden are more likely to achieve a deep response.
  - Extramedullary disease (outside of the bone marrow) is associated with a reduced response rate.
- **Lymphodepleting chemotherapy***
  - Patients who receive lymphodepleting chemotherapy have better responses.
  - The most effective chemotherapy regimen and dosing strategy are under study, but fludarabine plus cyclophosphamide is the most widely used regimen.
- **CAR T-cell levels following infusion**
  - Higher blood CAR T cell levels are often associated with a better initial response and durable remissions.

*Lymphodepleting chemotherapy is used to reduce a patient's number of circulating lymphocytes in order to make room for the CAR T cells.

Source: Adapted from Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. *Nat Rev Clin Oncol*. 2023;20(6):359-371. doi:10.1038/s41571-023-00754-1

The Future of CAR T-Cell Therapy. Researchers have started to rethink the source of immune cells to produce CAR T-cell therapies in order to potentially address some of the current limitations of this type of therapy. Using T cells collected from healthy donors or using umbilical cord blood are approaches used to produce "off-the-shelf" **allogeneic CAR T cells.**

The use of allogeneic CAR T cells has many potential advantages. These include decreased costs. The reduction in costs is due to the implementation of industrialized processes, which produce a large number of CAR T cells that can be produced from a single donor and become immediately available for treatment in cancer patients.

This approach is being pursued by several manufacturing companies and is under study in clinical trials for hematological malignancies, including B-cell ALL, AML, NHL and myeloma.

Patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find clinical trials and personally assist them throughout the entire clinical trial process.

Please call an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials and the Clinical Trial Support Center at LLS.

Clinical Trials for Blood Cancers

Every new drug for cancer, and for cancer complications such as GVHD, goes through a series of carefully controlled research studies before it can become part of standard care. These research studies are called "clinical trials" and they are used to find better ways to care for and treat people who have cancer. In the United States, the FDA requires that all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to:

- Treat cancer using
  - A new drug
  - A drug that has been approved, but to treat a different kind of cancer
  - A new combination of drugs
  - A new way of giving a drug—by mouth, intravenously (IV), etc.
- Prevent and/or manage treatment complications such as GVHD
- Manage cancer signs and/or symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back (recurring) after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new, cutting-edge therapies, and provide helpful information for future patients. The treatments and information we have today are due in large part to patients being willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit www.LLS.org/WhatToAsk for lists of suggested questions).
- Ask a family member or friend to go with you when you see your doctor—both for support and to take notes.

Clinical trials can be difficult to understand and to navigate, but The Leukemia & Lymphoma Society is here to help. Pediatric and adult patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find potential clinical trials, overcome barriers to enrollment and provide support throughout the entire clinical-trial process. Our Clinical Trial Nurse Navigators are registered nurses who are experts in adult and pediatric blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals
- Help you understand the clinical-trial process, including your rights as a patient
- Ask you for details about your diagnosis (such as past treatments, treatment responses, and your cancer genetic profile), your current health and your medical history, because these might impact whether you can take part in certain clinical trials
- Help you understand how your finances, insurance coverage, support network, and ability and willingness to travel might impact your choice of clinical trials
- Guide and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites

- Help deal with any problems you might have as you enroll in a trial
- Support you throughout the clinical-trial process

Please call an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials and the Clinical Trial Support Center at LLS.

Also, visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers.*

Feedback. To give suggestions about this booklet, visit www.LLS.org/PublicationFeedback.

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We're Here to Help

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 regions throughout the United States and in Canada. To find the region nearest to you, visit our website at www.LLS.org/LocalPrograms or contact an Information Specialist at (800) 955-4572.

LLS offers free information and services for patients and families affected by blood cancers. This section lists various resources you may find helpful.

For Help and Information

Consult with an Information Specialist. Information Specialists can assist you through cancer treatment and financial and social challenges, and provide accurate, up-to-date disease, treatment and support information. Our Information Specialists are highly trained oncology social workers and nurses. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. ET)
- Email and Live chat: www.LLS.org/InformationSpecialists

Clinical Trials (Research Studies). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Pediatric and adult patients and caregivers can work with our Clinical Trial Nurse Navigators who will help find clinical trials and provide personalized support throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

Nutrition Consultations. Schedule a free one-on-one nutrition consultation with one of our registered dietitians who have expertise in oncology nutrition. Consultations are available to patients of all cancer types and their caregivers. Dietitians can assist with information about healthy eating strategies, side effect management and more. Please visit www.LLS.org/nutrition for more information.

Free Information Booklets. LLS offers free education and support booklets for patients, caregivers and healthcare professionals that can either be read online or ordered. Please visit www.LLS.org/booklets for more information.

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

Financial Assistance. LLS offers financial support to eligible individuals with blood cancer for insurance premiums, co-pays, and non-medical expenses like travel, food, utilities, housing, etc. For more information, please:

- Call: (877) 557-2672
- Visit: www.LLS.org/finances

Resources for Families. Blood cancer occurs in a small number of children. Families face new challenges, and the child, parents and siblings may all need support. LLS has many materials for families, including a caregiver workbook, children's book series, an emotion flipbook, dry erase calendar, coloring books and a coloring app, a school re-entry program, and other resources. For more information, please:

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

Podcast. *The Bloodline* with LLS is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more

information and to subscribe to access exclusive content, submit ideas and topics, and connect with other listeners.

3D Models. LLS offers interactive 3D images to help visualize and better understand blood cell development, intrathecal therapy, leukemia, lymphoma, myeloma, MDS, MPNs and lab and imaging tests. Visit www.LLS.org/3D for more information.

Free Mobile Apps.

- LLS Coloring For Kids™ – Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit www.LLS.org/ColoringApp to download for free.
- LLS Health Manager™ – Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit www.LLS.org/HealthManager to download for free.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit www.LLS.org/SuggestedReading to find out more.

Connecting with Patients, Caregivers and Community Resources

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients and caregivers reach out and share information. Please visit www.LLS.org/chat for more information.

Local Programs. 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), local support groups and other great resources. For more information about these programs or to contact your region, please:

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

Advocacy and Public Policy. Working closely with dedicated volunteer advocates, LLS's Office of Public Policy elevates the voices of patients to state and federal elected officials, the White House, governors and even courts. Together, we advocate for safe and effective treatments. We pursue policies that would make care more accessible to all patients. And, most of all, we advocate for the hope for a cure. Want to join our work? Visit www.LLS.org/advocacy for more information.

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit www.LLS.org/ResourceDirectory to view the directory.

Additional Help for Specific Populations

Información en Español (LLS information in Spanish). Please visit www.LLS.org/espanol for more information. Language Services. Let members of your healthcare team know if you need translation or interpreting services if English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

Information for Firefighters. Firefighters are at an increased risk of developing cancer. There are steps that firefighters can take to reduce the risk. Please visit www.LLS.org/FireFighters for resources and information.

World Trade Center Health Program. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get help from the World Trade Center (WTC) Health Program. People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area and those who lived, worked or were in school in that area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a two-week period, you should contact a mental health professional. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter "depression" in the search box.

Resources

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 National Comprehensive Cancer Network® (NCCN)
www.nccn.org

The National Comprehensive Cancer Network®, a not-for-profit alliance of 26 of the world's leading cancer centers devoted to patient care, research, and education, is dedicated to improving the quality, effectiveness, and efficiency of cancer care so that patients can have the best quality of life. Through the leadership and expertise of clinical professionals at NCCN Member Institutions, NCCN develops practice guidelines that are appropriate for use by patients, clinicians and other healthcare decision-makers.

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