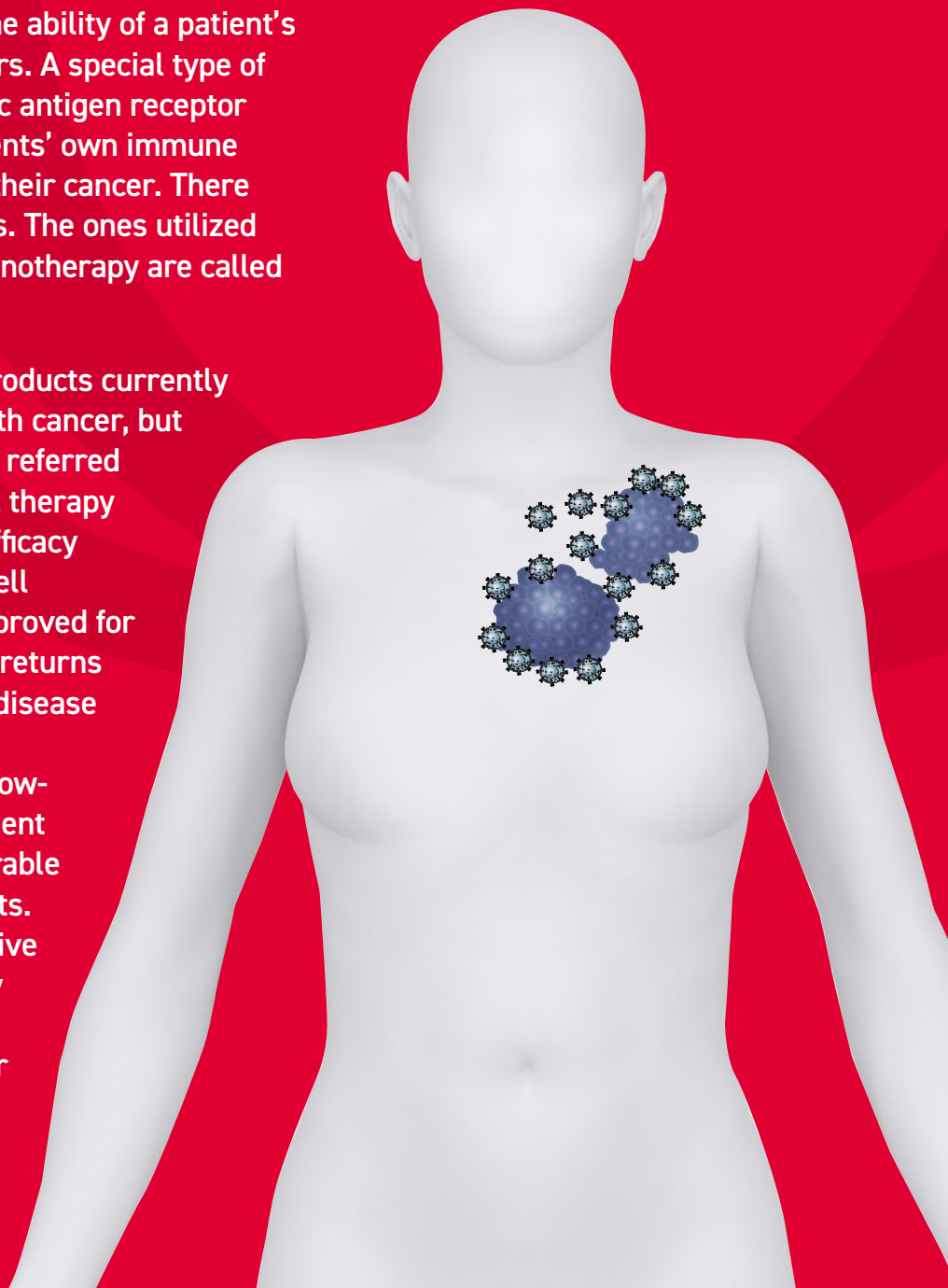


CAR T-cell Therapy for Lymphoma

Immunotherapy manipulates the ability of a patient's immune system to attack tumors. A special type of immunotherapy, called chimeric antigen receptor (CAR) T-cell therapy, uses patients' own immune cells and modify them to treat their cancer. There are many types of immune cells. The ones utilized for this particular type of immunotherapy are called T-lymphocytes or T-cells.

There are several CAR T-cell products currently approved for use in patients with cancer, but moving forward they will all be referred to as CAR T therapy. CAR T-cell therapy has demonstrated significant efficacy in patients with aggressive B-cell lymphomas and is now FDA approved for treatment of relapsed (disease returns after treatment) or refractory (disease does not respond to treatment) lymphomas. With a median follow-up of about 5 years, this treatment modality has demonstrated durable response in a number of patients. Patients with relapsed aggressive lymphoma who are functionally active and have no clinically significant co-morbidities (other medical problems) are eligible for CAR T-cell therapy.



The Process

1

Evaluation Before Treatment

CAR T-cell therapy is a complex procedure involving specialized care that is only offered to eligible patients at certified treatment centers.

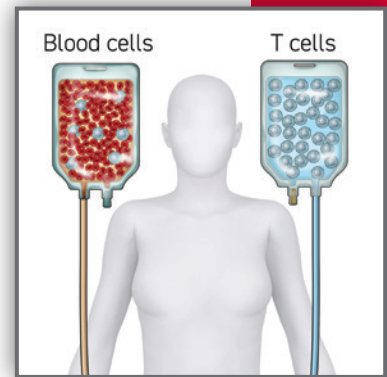
- The health care team will evaluate your fitness, medical history, current health status, type of lymphoma, and response to and type of previous treatments, as well as other treatment options, to decide whether you are a candidate for CAR T-cell therapy. They will compare the risks of the disease and the treatment and will discuss with you these expected risks and benefits.
- If you are considered a good candidate for CAR T-cell therapy, the health care team will refer you to a specialized treatment center. The health care team in the CAR T therapy treatment center will conduct their own evaluations to confirm whether you are a candidate for CAR T-cell therapy. This medical assessment considers the tissue biopsy (small sample of the affected tissue) showing the type of lymphoma, overall health, cardiac status (how your heart is working) , and current disease state and is followed by a psychosocial assessment that evaluates your support system and addresses potential barriers that may affect the procedure's success.

2

Leukapheresis

The first step of CAR T-cell therapy is to obtain some of your white blood cells. White blood cells work as part of the immune system to help the body fight infections. This process is called leukapheresis and usually takes about three to four hours.

- During leukapheresis, your blood is removed through a central catheter inserted underneath your collarbone (pheresis catheter) or an intravenous (IV) line in your arm.
- Your blood is then passed through a machine that separates your lymphocytes, including T-cells, from the other blood cells.
- The rest of your blood cells are returned to your body through the pheresis catheter or IV line inserted in your arm.

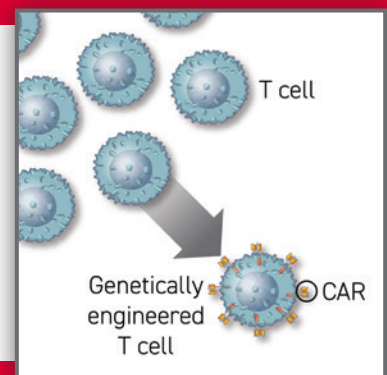


3

T-cell Engineering

The bag containing your white blood cells is sent to a processing center (lab) where the T-cells are separated from the rest of the white blood cells.

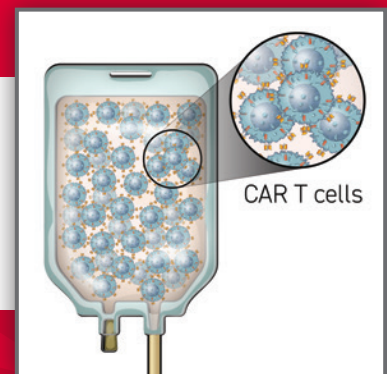
- The T-cells are then genetically modified to express a new protein, called the chimeric antigen receptor (CAR) on their surface and are transformed into CAR T cells. This reprograms your T-cells to recognize targets that are specific to lymphoma cells.
- Genetically reprogrammed CAR T-cells use this mechanism to fight your lymphoma.



4

CAR T-cell Transport

The engineered CAR T-cells are then grown at the processing center for approximately 2 - 6 weeks. The goal is to produce millions of new CAR T-cells. Once enough of the CAR T-cells are available, they are frozen for transport to your certified treatment center.



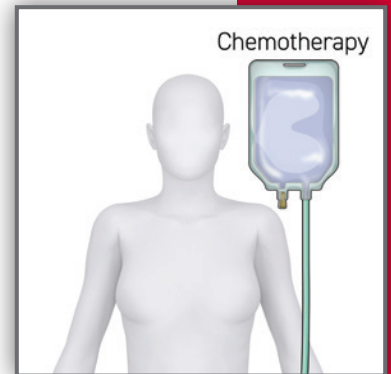
5

Lymphodepleting Chemotherapy

A few days prior to your CAR T-cell infusion, you will receive a short course (2 to 4 consecutive days) of chemotherapy as an outpatient. The two drugs most commonly given prior to CAR T-cell infusion are fludarabine and cyclophosphamide. This process is called lymphodepleting chemotherapy.

- The aim is to suppress your immune system slightly so that it does not reject your CAR T-cells once they are infused.
- This gives the infused CAR T-cells the chance to grow and expand in your body to fight your lymphoma.

While waiting for the CAR T-cells to develop, you might get treatment to control your lymphoma in the meantime (called bridging therapy).

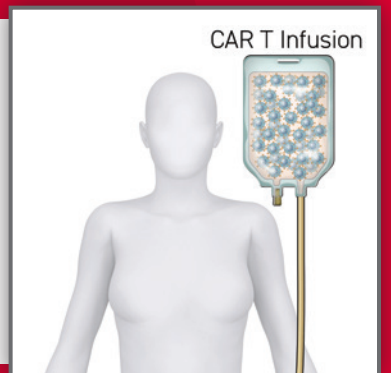


6

CAR T-cell Infusion

A day or two after completing chemotherapy, you will receive your CAR T-cells at your certified treatment center. This can be done as an inpatient or outpatient procedure, depending on the facilities available at your treatment center.

- The infusion of CAR T-cells takes only a few minutes.
- You may be given acetaminophen (Tylenol) and/or diphenhydramine (Benadryl) before the infusion to prevent allergic reactions to the preservative in the CAR T-cell product.

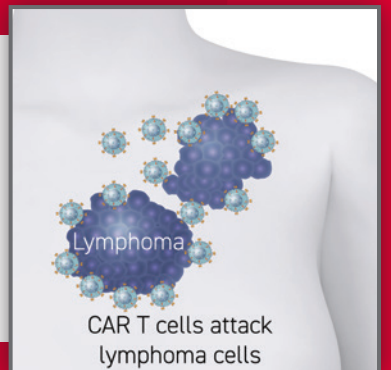


7

CAR T-cell Attacks the Lymphoma

Once the CAR T-cells enter your body, they begin to multiply and attack the lymphoma cells.

- It is important to remain under close observation by your healthcare team during the first 7 days, so that you can be monitored for symptoms like fever or neurologic side effects. These symptoms can happen as a result of chemicals called cytokines being released into the bloodstream after treatment with CAR T-cells.



8

Follow Up

After receiving the CAR T-cells, patients will need to remain in or near the certified treatment center for about four weeks to be monitored for side effects and treated, if needed. After that, patients will be monitored every few weeks or months (long-term follow up). The physician who treated the patient at the CAR T therapy center will also be in contact with the referring health care team to continue the patient's overall care.

After Receiving the CAR T-cells

After receiving the CAR T-cells, you will need to remain in or near the certified treatment center for about three to four weeks to be monitored for side effects and treated, if needed. Most patients will receive their CAR T-cells as an inpatient with close surveillance in the clinic. If it is done as an outpatient, you will need a caregiver, as you may not be able to care for yourself and it will not be safe for you to be alone for the first few weeks after the infusion. A recent study found that 30% to 40% of outpatients did not require hospitalization after receiving the CAR T-cell therapy. For CAR T-cells to be administered safely in the outpatient setting, the center must be prepared for patients to come to the hospital at any time. Not all patients are eligible for an outpatient setting, and this decision will depend on the product (Axi-cel is typically given as an inpatient), patient age (elderly patients may not be eligible), disease stage (how advanced is the lymphoma), presence of comorbidities and availability of housing near the treatment center.

For both inpatient and outpatient setting, the two major concerns after receiving CAR T-cell therapy are cytokine release syndrome (CRS) and neurotoxicity (see below). Side effects from CAR T-cell therapy usually range from mild to moderate in severity. Severe, life-threatening reactions are rare, but may be experienced by some patients. Be sure to ask your healthcare team which side effects you should contact them about, and when to call 911. If there is any question of what you are experiencing after receiving treatment, then it is important to always contact your healthcare team.

LRF's award-winning Focus On Lymphoma mobile app (lymphoma.org/mobileapp) and Lymphoma Care Plan (lymphoma.org/publications) can help patients manage documenting treatment side effects when speaking with your healthcare team.

CAR T-cell-specific Side Effects

Cytokine Release Syndrome (CRS)

Cytokine release syndrome (CRS) may occur as a systemic response to the CAR T-cell infusion. When the CAR T-cells attack the lymphoma cells, your immune cells are activated and release chemicals called cytokines which can induce inflammatory reactions. While cytokines are a natural part of your inflammatory response, a sudden release of a large quantity of cytokines can lead to CRS. This condition can be very serious and requires treatment by your doctor.

- The symptoms can include flu-like symptoms, fever, low blood pressure, hypoxemia (low levels of oxygen in the blood) and body aches.
- CRS usually occurs in the first few days to two weeks after the infusion of the CAR T-cells.
- Most CRS cases are treated with medications and other supportive treatments in the hospital. Severe CRS cases may require admission to an intensive care unit (rarely) and mechanical breathing support or dialysis (very rarely).
- Tocilizumab (Actemra) is approved by the U.S. Food and Drug Administration (FDA) to treat CAR T-cell-induced CRS. Corticosteroids can also be given for severe symptoms.

Neurological Effects

Neurological effects may occur between two days and three weeks after receiving the CAR T-cells, and usually follow CRS. These may include:

- Anxiety
- Delirium (a temporary mental state of confusion, reduced awareness of your environment, etc.)

- Dizziness
- Headache
- Insomnia (difficulty sleeping)
- Seizures (rare)
- Speech conditions (difficulty speaking)
- Tremor (shaking)
- Stroke

The precise cause of these symptoms is unknown, but they appear related to effects of the cytokines within the brain.

Because of these possible side effects, do **not** drive or engage in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least eight weeks after the procedure.

Neurological symptoms are treated with corticosteroids and anti-seizure medications such as levetiracetam (Keppra), if needed. Occasionally, the neurological symptoms can get worse and may require transfer to the ICU, along with a detailed evaluation by a neurologist.

Other Side Effects

Hypersensitivity is a condition where the body has an exaggerated response to a foreign (external) agent, and can occur during the CAR T-cell infusion. Other side effects may include severe or life-threatening infections, reactivation of hepatitis B viral infections, low white blood cell counts, low platelets, and low hemoglobin. As with many anticancer treatments, secondary malignancies (cancers occurring as a consequence of a prior therapy) are also possible.

Long-Term Side Effects

In most patients, the number of CAR-T-cells increases to a maximum level within two weeks then steadily decline. However, CAR T-cell therapy is unique in that the genetically modified cells can stay in your body for years, even if all the tumor cells are gone. Healthy cells in your body can also be targeted by your CAR T-cells; for example, healthy B-cells that express CD19 can be killed by CAR T-cells engineered to target CD19. This results in low levels or complete absence of healthy B-cells, decreased levels of antibodies, and increased risk of infection. This may be treated with the administration of antibodies to help keep you protected against infections. Patients may also develop bone marrow dysfunction and prolonged low blood cell counts, increasing the risk of infection. In this case, patients are treated with medication to prevent infection (prophylactic antimicrobials).

Outpatient Care

Identifying Lodging and Caregivers

Patients and caregivers must be aware of housing requirements prior to receiving treatment. Patients must stay close to the center for at least 4 weeks after the treatment, to be monitored for side effects and treated, if needed. Your healthcare team and social worker in the facility should be able to provide necessary guidance throughout all stages of treatment.

Patients should identify suitable primary and alternative caregivers prior to treatment. The healthcare team overseeing the treatment should then help select the person most qualified for the role. Overall, the caregiver:

- Should be at least 18 years of age, in good health, able to provide hands-on care, and available around the clock for a designated time frame

- Should be able to understand and recognize symptoms of CRS and neurotoxicity
- Should be able to measure patient's oral temperature and identify signs of neurologic impairment
- Should be able to communicate with the healthcare team whenever needed
- Transports or accompanies the patient to emergency and scheduled appointments
- Administers oral and potentially IV medications as instructed
- Prepares meals and keeps housing clean

Counseling on Leukapheresis and Bridging Therapy

Leukapheresis might reduce your blood calcium levels, which may cause numbness and tingling in the hands, feet and mouth, as well as muscle spasms. Your healthcare team can give you calcium through a drip to reduce these side effects. Eligibility criteria for leukapheresis may differ among treatment centers. Notify your healthcare team about any drugs you are receiving (including chemotherapy, steroids, or anticoagulants), as they may interfere with the process. Caregivers are encouraged to attend collection day, because patients are often fatigued and should not drive.

While your T-cells are being manufactured (which can take 2-6 weeks), you need to be monitored closely. During this time, you may receive bridging therapy (chemotherapy, radiation therapy or other lymphoma therapy given in the time between leukapheresis and infusion of CAR T-cells), steroids, radiation, and/or pain medications to help manage your symptoms. Ask your healthcare team in advance about standard home chemotherapy precautions, to help you and your caregiver prepare accordingly.

Educating on Acute and Long-term Toxicities

Patients and caregivers should learn to recognize acute episodes of CRS and neurotoxicity (see Side Effects section above), and to immediately contact their healthcare team if any of these symptoms appear. While severe cases may require temporary admission to an intensive care unit (ICU), these acute manifestations (side effects) are usually short-lived and reversible.

Recurrent CRS and neurotoxicity may occur throughout the first few weeks following CAR T-cells infusion. Patients should not drive or operate heavy machinery for 8 weeks after treatment. You may also experience persistent lower-than-normal blood cell counts (cytopenias) and infections.

CAR T-cell Therapies in Lymphoma

Approved CAR T-cell Therapies*

Axicabtagene Ciloleucel (Yescarta)

- Treatment targeting CD19 for adult patients with certain types of refractory or relapsed lymphoma after at least two other kinds of treatment.
 - Diffuse large B cell lymphoma (DLBCL) not otherwise specified
 - Primary mediastinal large B cell lymphoma
 - High grade B cell lymphoma
 - DLBCL arising from follicular lymphoma (transformed lymphoma)
 - Follicular lymphoma

Brexucabtagene Autoleucel (Tecartus)

- Treatment targeting CD19 for adult patients with relapsed or refractory mantle cell lymphoma (MCL). This is the first CAR T-cell therapy approved for the treatment of MCL.

Lisocabtagene maraleucel (Breyanzi)

- Treatment targeting CD19 for adult patients with large B-cell lymphoma who are refractory to first line chemoimmunotherapy or relapsed within the first 12 months of first line chemoimmunotherapy, relapsed/refractory disease after first line chemoimmunotherapy and are either eligible or not eligible for hematopoietic stem cell transplantation (due to comorbidities or age), and relapsed or are refractory after two or more lines of systemic therapy.
 - Large B-cell lymphoma, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma)
 - High grade B-cell lymphoma
 - Primary mediastinal large B-cell lymphoma
 - Follicular lymphoma grade 3B

Tisagenlecleucel (Kymriah)

- Treatment targeting CD19 for adult patients with certain types of large B cell lymphoma who have relapsed or were refractory (cancer does not respond to treatment) to two or more lines of systemic therapy.
 - DLBCL not otherwise specified
 - High grade B-cell lymphoma
 - DLBCL arising from follicular lymphoma
 - Follicular lymphoma

* In describing indications, the term "relapsed" refers to cancer that returns after treatment and "refractory" means that the cancer does not respond to treatment. Neither axicabtagene nor tisagenlecleucel can be used in patients with primary central nervous system lymphoma.

For the most recent information on approved CAR T-cell therapies, visit <https://lymphoma.org/aboutlymphoma/treatments/cartcell/>.

Investigational CAR T-cell Therapies

Several CAR T-cell therapies are in development for patients with lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The studies are also evaluating innovative approaches, including dual targeted and allogeneic CAR T-cell therapies. Please refer to Table 1 to find the latest information on clinical trials involving CAR T-cell therapies and lymphoma. In describing the type of treatment, the term "autologous" refers to the use of the patient's own cells and "allogeneic" means that the cells are collected from another donor (not the patient).

Table 1. Phase 2 or 3 clinical trials of CAR T-cell therapies in lymphoma

Drug	Type/Target	Condition
MB-106	Autologous therapy; CD20	r/r NHL
ALLO-501A	Allogeneic therapy; CD19	r/r Large B cell lymphoma
PBCAR0191	Allogeneic therapy; CD19	r/r NHL
PBCAR20A	Allogeneic therapy; CD20	r/r NHL r/r CLL/SLL

CLL/SLL; chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma.

The Benefits of Participating in a Clinical Trial

Clinical trials are not a "last resort" for patients. Every drug available today had to be tested in clinical trials before it was approved for general use, and all new and emerging treatments for lymphoma and CLL/SLL must be tested this way before patients can use them in the future. Clinical trials pose both benefits and risks for participants. Participating in a clinical trial can widen treatment options and provide access to new treatments that are not otherwise available to all patients. However, new treatments may or may not be as effective and safe as standard therapies. Patients who are randomized to the control group will receive the standard therapy that they would have received if they had not enrolled in the trial. All patients enrolled in a clinical trial are carefully monitored throughout the study.

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the Understanding Clinical Trials fact sheet on LRF's website at lymphoma.org/resources/educationresources/publications/ talk to their physician, or contact the LRF Helpline for an individualized clinical trial search by calling 800-500-9976, completing LRF's online clinical trials request form, or emailing helpline@lymphoma.org.

Commonly Asked Questions

Transplantation, Cell Therapies and Gene Therapy: What's the Difference?

Cellular therapy is the introduction of healthy human cells into the patient's body to replace or repair damaged tissue and/or cells. Examples of cell therapies include cellular immunotherapies, cancer vaccines, and stem cell transplantation.

Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. Gene therapies can work by replacing a disease-causing gene with a healthy copy, by inactivating a disease-causing gene that is not functioning properly or by introducing a new or modified gene into the body to help treat a disease.

A list of FDA-approved cellular and gene therapy products can be found in fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products.

How is CAR T-cell therapy different from stem cell transplantation?

Both stem cell transplantation and CAR T are forms of cellular therapy, and many of the steps in the procedures are similar. Stem cell transplants use blood forming stem cells collected from the patient (autologous transplant) or from a family member or unrelated donor (allogeneic transplant). Allogeneic transplants require immunosuppressant therapy to reduce the risk of rejection of the transplanted cells ("graft") and graft-vs-host disease (where the graft attacks the patient's healthy cells). The cells used in CAR T-cell therapy are genetically reprogrammed to recognize and fight cancer. Currently approved CAR T-cell therapies are exclusively autologous, but allogeneic approaches are under investigation (Table 1). While both procedures require prior chemotherapy, the regimen used in CAR T-cell therapy is associated with fewer side effects.

Is the procedure covered by insurance?

Before undergoing this procedure, check with your medical insurance provider to see what costs the provider will cover and what costs you will be responsible for paying. The medical center performing the procedure usually submits required information to determine if your insurance will cover these procedures. If there is a dispute about coverage or if coverage is denied, ask your insurance carrier about their appeals process. If a claim is repeatedly denied, contact your

state's insurance agency. CAR T-cell therapy should only be performed at certified centers, which may require travel and housing near the treatment center. Be sure to consider these costs and ask your provider if they cover these expenses.

If you need financial assistance, talk with your doctor and social worker about available options to enroll in an appropriate program. Cancer organizations like the Lymphoma Research Foundation (LRF) offer limited financial assistance to patients who qualify. Some pharmaceutical companies may have patient assistance programs in place that help to provide drugs to qualified patients, as well.

For additional information on financial aid resources, view LRF's Resources for Financial Assistance fact sheet available at lymphoma.org/publications or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

Which symptoms should I call my healthcare provider about or go to the emergency room for?

You will need to seek immediate attention for any of the following:

- Signs or symptoms associated with CRS including fever, chills, fatigue, rapid heartbeat, nausea, feeling short of breath, and feeling faint or dizzy upon standing.
- Signs or symptoms associated with neurologic events including altered mental state, sleepiness, memory loss, or personality changes, seizures, changes in your level of consciousness, difficulty writing, speech disorders, tremors, and confusion.
- Signs or symptoms associated with infection such as fever or chills.
- Signs or symptoms associated with bone marrow suppression including feeling overtired, bleeding that does not stop, or fever.

How can I be sure that I am getting my own CAR T-cell therapy?

There are several quality control checks throughout the process to make sure that you only receive your own CAR T-cells. Your T-cells are labeled with a unique identifier that stays with them during the entire process, and the identifiers are carefully matched to your identity before the cells are infused.

How long do I need to be near the certified treatment center?

You will need to plan to be near the certified treatment center (usually within one hour driving) for at least four weeks after the infusion of your CAR T-cells.

Can I take other medications at the same time as CAR T-cell therapy?

Before receiving the CAR T-cell therapy, tell your healthcare provider about all the medications, including the dosages, you currently take. Be sure to include prescription and over-the-counter medicines, as well as vitamins and herbal supplements. It is also important to tell your healthcare provider about all your medical history, including if you have or have had:

- Neurologic conditions (such as seizures, stroke, or memory loss)
- Lung or breathing conditions
- Heart conditions
- Liver conditions
- Kidney conditions
- A recent or active infection

Questions To Ask Your Doctor

- Would CAR T-cell therapy be a good treatment option for me? Would choosing this treatment prevent me from getting a different kind of treatment at a later point?

- What is the chemotherapy that I will be receiving prior to the CAR T-cell therapy?
- What is the goal of this treatment? What are the expected benefits?
- Will I require bridging therapy? If so, what type?
- How will we know if the CAR T therapy is working? What tests will I need to determine if treatment is working, and how often will I need to be tested?
- What are the risks and possible side effects of each treatment? Can these side effects be prevented or controlled?
- How will this treatment affect my normal daily activities (work, driving, childcare, etc.)?
- What should I do to take care of myself during and after treatment?
- Will I still be able to work?
- Do I need a caregiver while I am in treatment? What should I do if I'm having trouble identifying a caregiver?
- Can you make recommendations to fulfill the outpatient lodging requirements?
- What should my caregiver know and how should he/she prepare?
- Are there any medical conditions that would exclude me from getting CAR T-cell therapy?
- What is a clinical trial? Are clinical trials available that are studying new treatments for my type of NHL? Would a clinical trial be appropriate for me? How would I benefit?
- How much will this treatment cost and are there any financial assistance resources? Will my insurance cover it?

LRF's Helpline and Lymphoma Support Network

The LRF Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. LRF also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

Para información en Español, por favor visite lymphoma.org/es. (For Information in Spanish please visit lymphoma.org/es).

LRF Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their caregivers with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more this resource, visit our website at lymphoma.org/mobileapp, or contact the LRF Helpline at 800-500-9976 or helpline@lymphoma.org.

Lymphoma Care Plan and Patient Education Programs

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. LRF's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting lymphoma.org/ publications. LRF also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. To view our schedule of upcoming programs, please visit lymphoma.org/programs.

Finding a Treatment Center

CAR T-cell therapy is only offered to eligible patients at certified treatment centers. For more information about certified medical centers in the US that offer CAR T-cell therapy, visit bmtinfonet.org/car-t-cell-therapy-center-directory, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org

Resources

LRF offers a wide range of free resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and CLL/SLL including our award-winning mobile app. LRF also provides many educational activities, including our in-person meetings, podcasts, webinars for people with lymphoma, as well as patient guides and e-Updates that provide the latest disease-specific news and treatment options. To learn more about any of these resources, visit our website at www.lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.



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