LEUKEMIA & LYMPHOMA SOCIETY®

CART Effects

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

Patients who have been treated with CAR T-cell therapy have reported mild to moderate side effects: however, this treatment is sometimes associated with significant, serious side effects. It is important that you speak with your doctor about potential side effects before you start any treatment.

Most side effects resulting from CAR T-cell therapy will either resolve on their own or they can be managed with appropriate treatment. The most common potential side effects of CAR T-cell therapy are cytokine-release syndrome; macrophage activation syndrome; neurologic toxicities; tumor lysis syndrome; anaphylaxis (life-threatening allergic reaction); and B-cell aplasia. A description of each of these side effects follows, along with suggested strategies to minimize or counteract them.

Cytokine-Release Syndrome (CRS)

What is it?

Cytokines (chemical messengers that help the T cells carry out their functions) are produced when the CAR T cells multiply in the body and kill cancer cells. With CAR T-cell therapy, when the CAR T cells encounter their targets, they are rapidly activated. At this point, numerous inflammatory cytokines are released. Mild to potentially life-threatening symptoms are caused by the large amounts of cytokines that are produced and then released by the activated immune system. This collection of symptoms is known as “cytokine-release syndrome.”

How long does it last?

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; it depends on the type of intervention used to manage it.

What are the symptoms?

Mild flulike symptoms	More serious symptoms
Nausea Fatigue Headache Chills Fever	Low blood pressure Tachycardia (abnormally rapid heart rate) Capillary leakage (fluid and proteins leak out of tiny blood vessels and flow into surrounding tissues, resulting in dangerously low blood pressure) Cardiac arrest Cardiac arrhythmias Cardiac failure Hemophagocytic lymphohistiocytosis (life-threatening immune system activation)/ macrophage activation syndrome (life-threatening activation of macrophages) (HLH/MAS) (see *Macrophage Activation Syndrome (MAS),* on *page 2*) Hypoxia (lack of oxygen reaching the tissue) Renal insufficiency (poor function of the kidneys) Poor lung oxygenation Multiple organ failure Neurological symptoms (see *Neurologic Toxicities,* on *page 2*)

What is the treatment?

Severe CRS requires intensive care treatment. Most symptoms are reversible, but the potential life-threatening risk of CAR T-cell therapy should not be underestimated. Deaths have been reported in CAR T-cell trials.

Depending on its severity, CRS can require only supportive care with fever-reducing medication and intravenous (IV) fluids or it may require rapid intervention with immunosuppressive anticytokine-directed therapy and/or corticosteroids. 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.

Fortunately, research has shown that CRS can be mitigated (lessened) by the infusion of **tocilizumab (Actemra®)**, which reduces inflammation without compromising the effectiveness of T cells. Tocilizumab is approved by the US Food and Drug Administration (FDA) for the treatment of adults and pediatric patients 2 years of age and older with CAR T-cell-induced severe or life-threatening CRS symptoms.

If severe CRS symptoms do not improve with tocilizumab, or symptoms are rapidly getting worse, corticosteroids are used to reverse CRS. It is not known whether high dosages of corticosteroids affect the ability of CAR T cells to completely destroy the cancer cells, but patients who have received corticosteroids have achieved long-lasting remissions. When CRS is life threatening, these drugs may be the only way to stop the worsening symptoms. Your doctor may also prescribe **siltuximab (Sylvant®)** as a treatment for CRS.

Macrophage Activation Syndrome (MAS)

This syndrome is closely associated with severe CRS. It is a condition caused by the excessive activation and multiplication of T cells and macrophages and it is generally seen in patients with chronic autoimmune and rheumatic diseases. Fortunately, research has shown that MAS (like CRS) can be mitigated (lessened) by the infusion of the monoclonal antibody **tocilizumab (Actemra®)**. Corticosteroids and anticytokine therapy can be considered as treatment options if MAS symptoms are severe and the patient's condition is not improving.

Neurologic Toxicities

The connection between CRS, MAS and neurologic adverse events is not yet completely understood. The frequency, severity and nature of neurological effects appear to be different depending on the CAR T-cell product. This could be due to differences in the product, or due to the small number of patients who have undergone CAR T-cell therapy and been studied so far, or to both of these reasons. These side effects have been observed in the CAR T-cell treatment of acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL) and myeloma. Common symptoms include

- Language impairment (aphasia)
- Confusion
- Delirium
- Involuntary muscle twitching
- Hallucinations
- Unresponsiveness
- Seizures.

The underlying cause is unclear and it is not known whether the presence of CAR T cells in the central nervous system is related to the occurrence or severity of neurotoxicity. The cause of neurotoxicity is the subject of intense investigation by researchers.

Neurotoxicity has been reversible in most cases and the symptoms have resolved over several days without intervention or apparent long-term effects. However there can be life-threatening adverse neurological events and there have been fatalities resulting from neurologic complications of CAR T-cell therapy, notably cerebral edema (swelling in the brain). Some symptoms of neurologic toxicity have been treated with anti-epileptic medication and/or corticosteroids. Some patients may receive prophylactic (preventative) medications, such as **levetiracetam (Keppra®, Keppra® XR, Spritam®)**. More study is needed to understand the mechanism of action, associated risk factors and best management of this potential side effect.

Tumor Lysis Syndrome (TLS)

Another known side effect of CAR T-cell therapy is TLS, a group of metabolic complications that can occur due to the breakdown of dying cells—usually at the onset of toxic cancer treatments. However, the onset of TLS can be delayed and may occur one month or more after CAR T-cell therapy. Tumor lysis syndrome can cause damage to organs, such as the kidneys, and can be a life-threatening complication of any treatment that causes breakdown of cancer cells, including CAR T cells. The complication has been managed by standard supportive therapy, including hydration and the use of the medications **allopurinol (Zyloprim®, Aloprim®)** and **rasburicase (Elitek®)**.

Anaphylaxis (Life-threatening Allergic Reaction)

There is potential for a patient receiving CAR T-cell therapy to have an overwhelming immune response (called "anaphylaxis") against the CAR itself. Symptoms associated with an anaphylactic reaction include hives, facial swelling, low blood pressure and respiratory distress. There have been a few reports of acute anaphylaxis. Thorough monitoring and immediate treatment of this life-threatening side effect are critical for patients receiving CAR T-cell therapy.

B-cell Aplasia

Chimeric antigen receptor T-cell therapy targeting antigens found on the surface of B cells not only destroys cancerous B cells but also normal B cells. Therefore, B-cell aplasia (low numbers of 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 side effect also reduces the body's ability to make the antibodies that protect against infection. Intravenous or subcutaneous immunoglobulin replacement therapy may be given with the aim of preventing infection, especially in patients with recurrent or severe infections. B-cell depletion has been reported in nearly all patients treated with CD19-targeted CAR T cells and depending on the CAR T-cell configuration, B-cell aplasia can last from months to years. Long-term follow-up study is needed to assess the late effects of B-cell aplasia.

For more information about CAR T-cell therapy, please visit www.LLS.org/Booklets to see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts*.

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