CAR T-cell therapy: weaponizing the immune system to fight cancer

With genetic engineering, patients' own cells become their cancer treatment

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In recent years, immunotherapy has joined surgery, chemotherapy and radiation as a treatment option for many forms of cancer. One type of immunotherapy, chimeric antigen receptor (CAR) T-cell therapy, has delivered exciting results for people whose cancer didn't respond to previous treatment.[1] It shows promise for other forms of cancer, as well.[1]

In CAR T-cell therapy, white blood cells are taken from the patient and genetically engineered to help the immune system fight cancer, using adoptive cell transfer (ACT).[2,3]

So far, those treated with CAR T-cell therapy are patients who had roughly six months left to live, after traditional treatment failed.[1] CAR T-cell therapy produced early remissions in more than 80% of those patients with B-cell acute lymphoblastic leukemia (ALL) and in nearly half of those with B-cell non-Hodgkin's lymphoma (NHL).[2]

The immune system and CAR T-cell therapy

The immune system defends the body against infection and cancer. Lymphocytes, a type of white blood cell, play a major role. There are three types of lymphocytes:[4,5]

1. B cells, which make antibodies to fight infection
2. Natural killer cells, which attack infected cells and destroy viruses
3. T-cells, which seek out and destroy any abnormal cells, including cancer

When cancer cells manage to elude the immune system's response, the immune system must be retrained to recognize the invading cells and mount a successful counterattack.[5]

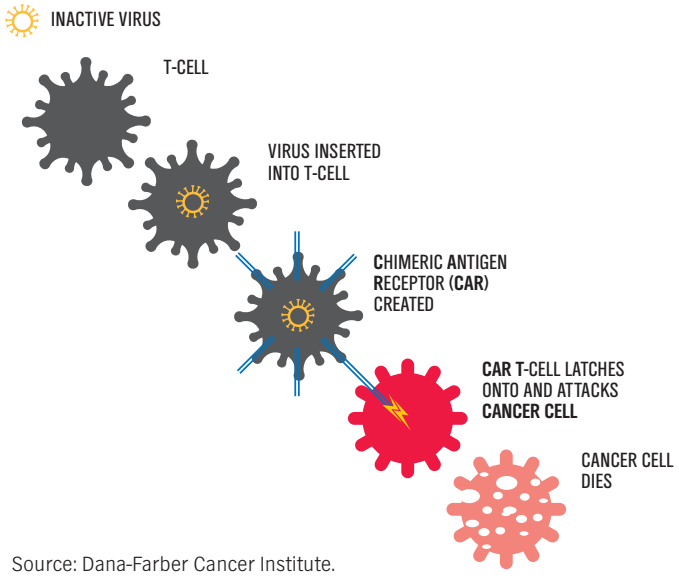
CAR T-cell therapy involves taking T-cells from the patient and "training" them by genetically modifying them to recognize and kill the specific cancer in the patient's body.[6] In a successful CAR T-cell treatment, the specially trained T-cells are reintroduced to the patient's bloodstream and quickly overwhelm and destroy the cancer cells.[1]

Which types of cancer can be treated with CAR T-cell therapy?

The U.S. Food and Drug Administration (FDA) has approved CAR T-cell therapies to treat adult B-cell non-Hodgkin's lymphoma and childhood acute lymphoblastic leukemia in patients who have already been through two unsuccessful treatments, such as chemotherapy, radiation or stem-cell transplant.

Ongoing clinical trials are evaluating CAR T-cell therapy to determine whether it's appropriate as a first or second line of treatment.[1]

THE MAKING OF A **CAR T-CELL ATTACK**



Source: Dana-Farber Cancer Institute. *What's Next in CAR T-Cell Therapy?* (June 1, 2018): blog.dana-farber.org.

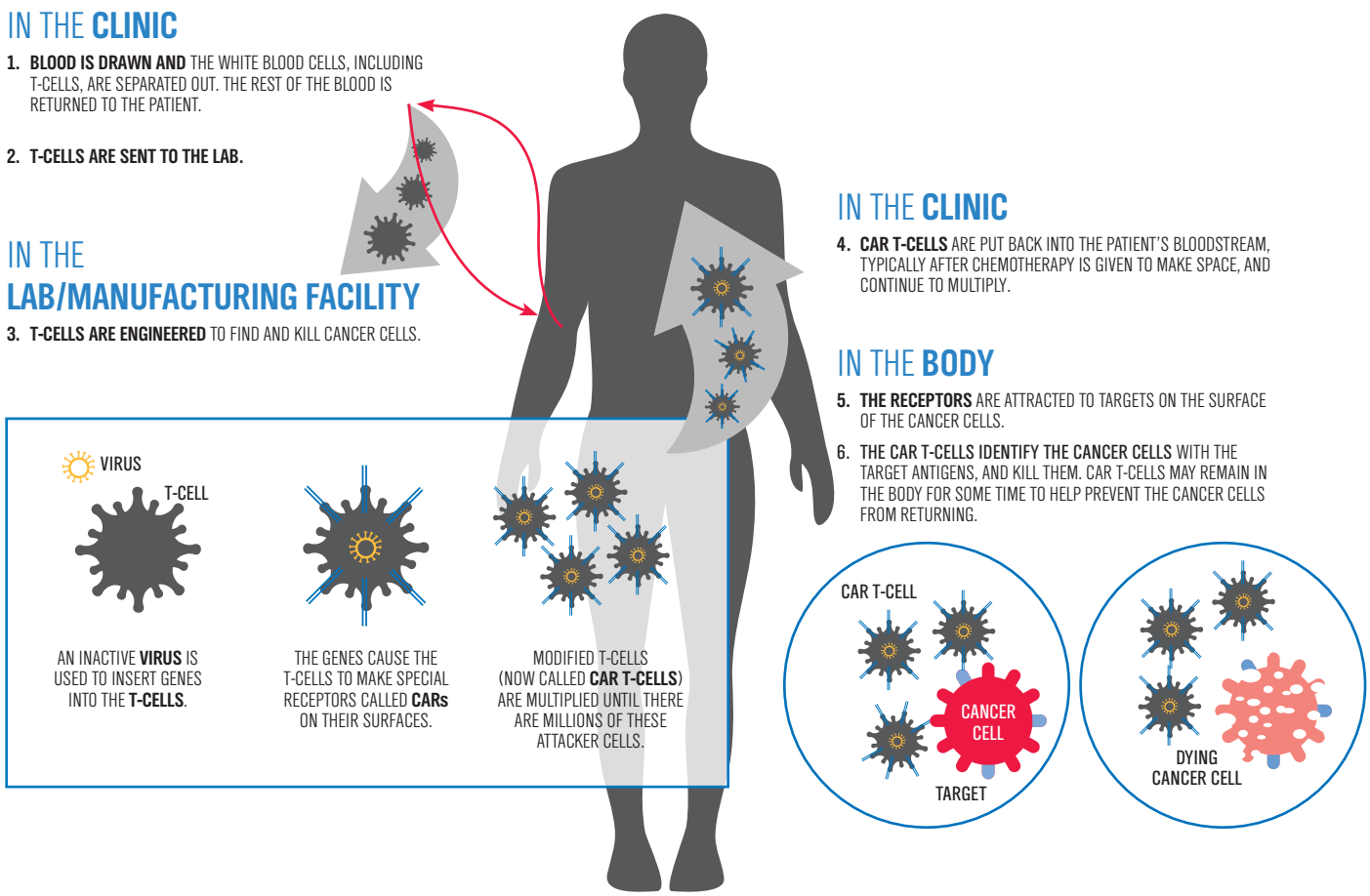
How does CAR T-cell therapy work?

First, the patient's T-cells are collected via leukapheresis. An intravenous catheter is inserted into a vein to collect the patient's blood. The T-cells are extracted, and the rest of the blood is returned to the patient's body. The process takes three to six hours.[3,4,7,8] The extracted T-cells are, then, frozen and sent to a laboratory or drug manufacturing facility.

At the lab, by introducing DNA using a disarmed virus, the cells are re-engineered to sprout CARs on their surfaces.[3,4,5] These special receptors enable T-cells to recognize and attach to a specific antigen or protein on a cancer cell.[3] Once CARs emerge, T-cells become CAR T-cells, able to produce chemicals that kill cancer.[1]

The next step is to multiply the re-engineered CAR T-cells until there are hundreds of millions of them.[3] Once there are enough, the cells are frozen and returned to the hospital or center where the patient is being treated.[4] This process generally takes three to four weeks,[7,8] but, with advances in production, some labs are able to return CAR T-cells in about a week.[3]

During this time, the patient is given chemotherapy, called lymphodepletion, to prepare for the infusion of thawed CAR T-cells.[4] Once they're reintroduced to the patient's body, CAR T-cells continue to multiply, becoming an army that attacks and destroys any cells with the targeted antigen.[3,5] Even after CAR T-cells wipe out all of the cancer cells, they remain in the body for some time, and may protect against recurrence.[4]



Source: Leukemia and Lymphoma Society. *Chimeric Antigen Receptor (CAR) T-Cell Therapy* (accessed July 2018): lls.org.

What are the risks of CAR T-cell therapy?

The most common side effect of CAR T-cell treatment is cytokine release syndrome (CRS), also called a "cytokine storm."[1] Other potential side effects include neurological symptoms, B-cell aplasia, tumor lysis syndrome, anaphylaxis and cerebral edema.

Cytokine release syndrome

Cytokines are proteins that help transmit messages from one cell to the cells and tissue around it. For T-cells, cytokines activate other white blood cells to fight off cancer and infection, and signal them to move toward areas of inflammation.[6]

Usually, cytokine signaling stops once the unhealthy cells have been destroyed, but sometimes the response continues out of control, activating more and more white blood cells — leading to a cytokine storm.

While CRS is considered an adverse effect — and can be very dangerous — it's so common that doctors view it as a sign that the treatment is working.[3] About 70% to 90% of patients treated with CAR T-cell therapy experience CRS.[1]

CRS symptoms typically appear two to three days after the CAR T-cell infusion, but can appear any time within the first three weeks.[4] For most patients, it feels like a severe case of the flu and lasts about a week.[1] Symptoms include:[1,3,4,6]

Less serious

- High fever
- Fatigue
- Body aches
- Nausea
- Headache
- Chills

More serious

- Low blood pressure
- Tachycardia (rapid heart rate)
- Capillary leakage
- Cardiac arrest
- Abnormal heart rhythm
- Heart failure
- Impaired kidney function
- Swelling
- Lack of oxygen to organs and tissue
- Severe tissue damage
- Multiple organ failure

Most symptoms are reversible, but severe CRS requires treatment in intensive care. Occasionally, CRS symptoms are so severe that the patient doesn't survive.[4] Fortunately, doctors are having success in treating CRS with tocilizumab (Actemra®), a drug most often prescribed for rheumatoid arthritis. Tocilizumab is now FDA-approved for CRS, and reverses the symptoms quickly in most cases.[1]

Neurological symptoms

CAR T-cell therapy patients may experience neurological changes after treatment. Sometimes, this is called CAR T-cell-related encephalopathy syndrome (CRES). In most cases, these symptoms are temporary and go away on their own within a week.[1,3] However, sometimes the neurological effects can be life-threatening.[3] Neurological side effects include:[1]

- Confusion
- Disorientation
- Language impairment; inability to communicate
- Involuntary muscle movements
- Hallucinations or delirium
- Unresponsiveness
- Seizures

B-cell aplasia

The antigen targeted by CAR T-cells is also found on normal B cells, so CAR T-cell treatment often results in a mass B-cell die-off.[3] The resulting shortage of B cells, called B-cell aplasia, leaves the patient vulnerable to infection. B-cell aplasia can be treated with immunoglobulin therapy, which provides the antibodies the patient's immune system needs to fight off infection.[3]

Tumor lysis syndrome

Cancer treatments that lead to a large number of dying cells breaking down at once can cause a group of metabolic complications called tumor lysis syndrome (TLS). While TLS can usually be managed with supportive care, it can cause life-threatening organ damage.[4]

Anaphylaxis

Rarely, a patient will suffer a life-threatening allergic reaction to the infused CAR T-cells. This is called anaphylaxis. Doctors monitor patients closely following a CAR T-cell infusion to watch for any symptoms, like hives, facial swelling, low blood pressure and trouble breathing.[4]

Cerebral edema

In some clinical trials, patients suffered from swelling in the brain, called cerebral edema. Cerebral edema can be life-threatening. Fortunately, this side effect is rare and has not been seen in most clinical trials.[3]

What CAR T-cell treatments are available?

The FDA has approved two CAR T-cell therapies:[3]

- **KYMRIAH®** (tisagenlecleucel), by Novartis, was approved in 2017 for treating children and young adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). In 2018, it was approved for adults with relapsed or refractory diffuse large B-cell lymphoma.[9] It's available in 52 treatment centers across the U.S.[7]
- **YESCARTA®** (axicabtagene ciloleucel), by Gilead, was approved in 2017 for adults with relapsed or refractory large B-cell lymphoma.[4] It's available in 61 treatment centers in the U.S.[8]

The availability of treatment centers poses a significant obstacle. Patients who are already very ill need to travel to a treatment center, in some cases many hours away. For a week after infusion, patients are monitored daily for complications at the center where they received treatment, and are required to stay within two hours of the treatment center for the next four weeks.[8] Travel and lodging costs alone can be prohibitive. Patient assistance programs are available from both Novartis and Gilead to help with some of these expenses.[7,8]

Challenges to the health care industry

CAR T-cell therapy is a medical breakthrough, and has also broken new ground in treatment costs. A single infusion with KYMRIAH® is priced at $475,000 — not including pretreatment, hospitalization or any costs associated with complications or follow-up care. Based on information collected during clinical trials, the average cost for a year of KYMRIAH® treatment is $547,000.[10]

The only other treatment option is allogeneic stem-cell transplant, which comes with a first-year price tag of up to $800,000, as well as high-cost follow-up care for years after transplant. CAR T-cell therapy generally requires fewer hospitalizations and outpatient visits compared to stem-cell transplant, lessening strain on the health care system and on patients, families and caregivers.[10]

Insurers agree the treatment is beneficial, but paying for it is a challenge as payment systems haven't kept pace with new technology. Current reimbursement systems are built to account for extra costs incurred during outpatient infusions or hospitalizations, but not treatments that combine both. "Infusion" reimbursements don't begin to cover the cost of a lengthy hospitalization and intensive care stay, and a lump-sum hospitalization reimbursement doesn't cover the complex and expensive infusion itself.[11] Insurers say CAR T-cell treatments aren't affordable unless they can spread the cost over time. But hospitals have expended their resources upfront and can't wait for reimbursement indefinitely.[11]

Insurers, hospitals, the U.S. Centers for Medicare & Medicaid Services and CAR T-cell drug manufacturers are working toward a reimbursement model that ensures this vital therapy is available to people who need it.[11,12]

The future of CAR T-cell therapy

Moving forward, CAR T-cell research will focus on making the therapy safer and more accessible, and applying it to other types of cancer. With multiple drug manufacturers and research organizations working to improve and expand on CAR T-cell technology, the future is promising.

Improving safety

The post-infusion cytokine storm is the most dangerous adverse event associated with CAR T-cell treatment, so future CAR T-cells will be developed with built-in controls to regulate cytokine activity.[6] Some potential solutions in development include:

- **Decoy molecules** that bind to some of the proteins in the cytokine pathway to stop the response from spinning out of control. The molecules, called peptides, interfere with the cytokine signaling pathway and can reduce cytokine production by roughly 70%.[6]
- **Immune checkpoint inhibitors** to stop and start the CAR T-cells' response. Administered along with the CAR T-cell infusion, an immune checkpoint inhibitor activates CAR T-cells to attack cancer. If a cytokine storm begins, it can be stopped immediately, deactivating CAR T-cells and halting cytokine release.[2,6]
- **Predictive biomarkers** that suggest a patient is more likely to suffer severe side effects from treatment, allowing their doctors to intervene early.[13]
- **Bispecific CARs** that target two different proteins for a two-step verification process. Two types of CARs are engineered into each CAR T-cell. One behaves as usual, targeting the protein found on cancer cells. The other, called an inhibitory CAR (iCAR), is activated by an antigen found only on healthy cells. This allows for safer CAR T-cell treatment, preventing CAR T-cells from inadvertently attacking healthy cells. If an iCAR is activated by a "healthy" protein, it sends an inhibitory signal to disable the other CAR.[8]

Improving effectiveness

While CAR T-cell therapy is very effective, up to a third of patients relapse within a year of treatment.[3] This can be due to CAR T-cells dying off naturally, cancer cells mutating and losing the target antigen or CAR T-cells prematurely stopping their attack on the target antigen.[4] In clinical trials, immune checkpoint inhibitors are being used to reactivate any CAR T-cells that remain in the body long after infusion, to launch another attack.[2] And compound CAR T-cell treatment targets more than one cancer cell antigen to ensure cancer cells that lose one target antigen aren't missed.[14]

Fine-tuning timing

Doctors and researchers are investigating whether CAR T-cell therapy earlier in a patient's treatment can match or exceed the effectiveness of chemotherapy or stem-cell transplant. Currently, CAR T-cell patients must have already received at least two other therapies without achieving remission. Doctors hope to be able to identify patients for whom traditional therapies are unlikely to succeed, and move them more quickly to CAR T-cell therapy.[1,2] If CAR T-cell therapy is proven to be as successful as other treatments, it may be more cost-effective overall and allow patients a faster return to their normal lives.[1]

Improving accessibility

Current CAR T-cell treatments use the patient's cells, but using T-cells from healthy donors would allow for faster treatment and could drive down the cost of CAR T-cell therapy.[2,3] The risk is that patients' immune systems would quickly attack these "off-the-shelf" donor cells, or that CAR T-cells would attack patients' healthy tissue. However, European trials with donor cells have been successful.[3]

Broadening treatment to other types of cancer

Treatment of other blood cancers with CAR T-cell therapy is showing promising results, and researchers are developing CAR T-cell treatments for solid tumors, as well.[4]

CAR T-cell therapy will continue to improve as doctors and researchers discover more ways to customize treatment to each patient. As clinical trials progress, outcomes for cancer patients will only get better.

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