LYMPHOMA CANADA

CAR-T: Science Overview

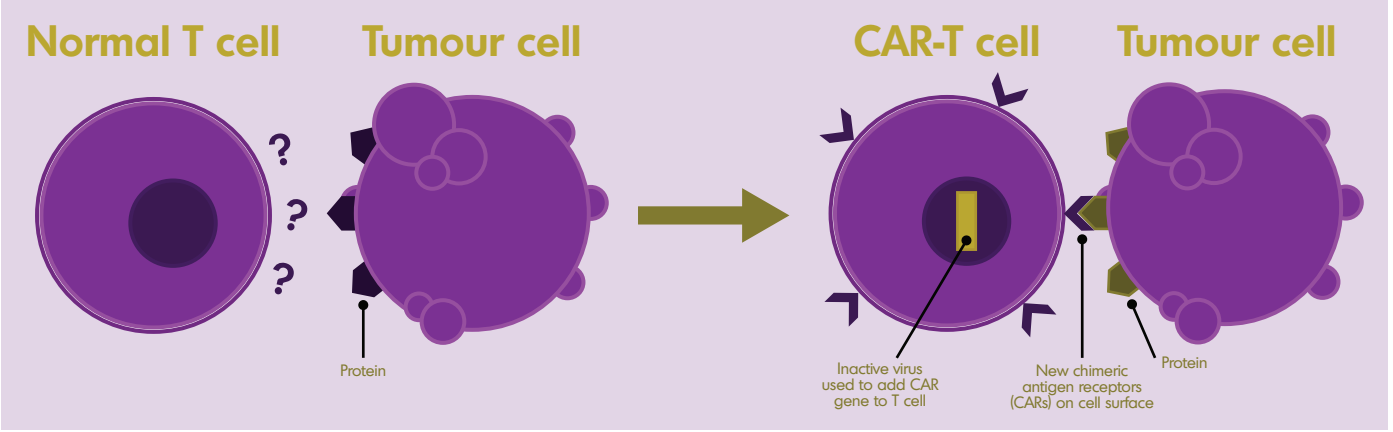
CAR-T Overview

Chimeric Antigen Receptor T cell therapy, or CAR-T therapy, is a type of immunotherapy that modifies a patient's T cells to better detect and destroy lymphoma. A part of the body's immune system, T cells are a type of white blood cell that attacks virus-infected cells, foreign cells and cancer cells. CAR-T therapy enhances the effectiveness of T cells.

CAR-T therapy uses genetic engineering to alter a patient's T cells. A virus is used to penetrate the T cell and genetic material is inserted. This produces transmembrane proteins on the T cell's surface that recognize specific proteins in the tumour. The target for CAR-T therapy can be chosen when the cells are being engineered. Currently, CAR-T therapy against CD19 (a marker seen in most B cell lymphomas) has become a new, standard treatment.

With current CAR-T therapies, two signals are created through CAR-T cells: one activates the T cell when it binds to the tumour's protein; the second stimulates cellular replication, which ensures a significant supply of chimeric T cells in the patient.

Mechanism of action of CAR-T cells.



CAR-T Protocol

There are six steps in the CAR-T protocol:

1 Screening

Patients consult with their physician to see if they are medically eligible for CAR-T therapy. This may include submitting medical records to the specialty laboratory that manufactures the CAR-Ts.

2 Leukapheresis

Blood is taken from the patient and the T cells are isolated and removed in a process called apheresis or leukapheresis. The remaining blood is transfused back to the patient.

Timeline: The procedure takes 3 – 6 hours

3 T-Cell Engineering

The T cells are shipped to a designated laboratory where they are genetically modified with inactive viruses into CAR-Ts and expanded. The modified cells are shipped back to the patient's treatment centre.

Timeline: Approximately 2 – 4 weeks

For more detailed information about CAR-T potocol, please read Lymphoma Canada's CAR-T Protocol Overview.

4 Pre-Treatments

Patients are typically given low-dose chemotherapy called lymphodepleting chemotherapy to reduce their number of immune cells before the CAR-Ts are infused. This helps the CAR-Ts start to grow and multiply within the patient. The patient may receive bridging treatment with steroids, radiation or chemotherapy to help keep their cancer in check while waiting for CAR-T therapy.

Timeline: Approximately 2–14 days before the CAR-T infusion

5 CAR-T Infusion

The modified CAR-T cells are infused into the patient at their treatment centre.

Timeline: 30 - 60 minutes

6 Observation

Patients are monitored regularly to see if the CAR-T therapy is effective and for short- and long-term side effects of CAR-T therapy. Patients are advised to stay near their treatment centre for a few weeks, typically one month. Most short-term side effects can be managed with supportive therapies.

It is important patients and caregivers can identify symptoms quickly so they can be treated. (See more information about side-effects on page 4.)

Timeline: 30 - 60 minutes

Who is CAR-T for?

CAR-T currently treats some aggressive subtypes of lymphoma. In addition to subtype and stage, physicians will also assess the patient's overall health, fitness and circumstance for this treatment. This may include the patient's comorbidities, the associated ability to withstand the vigorous treatment, and their willingness and ability to travel for treatment.

There are specific eligibility criteria for each CAR-T therapy, based on what was learned in clinical trials and regulatory approvals.

Generally speaking, the following patients are eligible for CAR-T therapy :

- Were diagnosed with a subtype of lymphoma for which the CAR-T therapy is approved
- Meet regulatory criteria (e.g. relapsed twice and have been previously treated)
- Have tumours that express the specific antigen the therapy targets
- Satisfactory organ function and performance status
- No active infections
- No significant cardiac, neurological or immune dysfunction

Physicians will discuss patient's eligibility and will send relevant medical records to the specialty cancer centre that performs the CAR-T therapy to be evaluated for treatment.

Clinical Effectiveness

Understanding patient outcomes after treatment with CAR-T therapy is important because while the initial results for some patients are positive, clinical effectiveness varies considerably amongst patients. The ideal patient candidate is still under trial. Some patients achieve long-term durable remission, but CAR-T therapy is not currently considered a cure as more data is needed to see if patients who achieve a full remission stay disease-free long-term.

The outcomes measured in clinical trials include:

Complete response rate (CR)

- The percentage of patients who respond to treatment with the disappearance of all signs of cancer. Even if patients do not achieve CR, they could experience a partial response (PR). Overall response rate (ORR) is the sum of CR and PR.

Median overall survival (mOS)

- The median length of time from the date of diagnosis or the start of treatment that patients are still alive.

Progression-free survival (PFS)

- The length of time during and after treatment that a patient lives with disease but it does not progress or get worse.

Side Effects

There are several short- and long-term side effects related to CAR-T therapy. Patients are advised to stay near their treatment centre for a few weeks. Most short-term side effects can be managed with supportive therapies. However other side effects can be more serious and potentially life-threatening and may require treatment in a hospital intensive care unit.

Cytokine Release Syndrome

As CAR-T cells are released and multiply in the patient's body, their immune system is highly activated and releases a massive number of inflammatory cytokines into the blood, causing cytokine release syndrome (CSR). This can happen within the first week after infusion or later in some cases.

The duration and intensity of CSR can vary. Some patients only experiencing mild flu-like symptoms while others have high fevers, hypoxia (oxygen deficiency), low blood pressure and multi-organ toxicity.

Neurotoxicity (now termed IEC-associated neurotoxicity syndrome or ICANS)

IEC refers to Immune Effector Cells. The CAR-T cells can have an effect on the patient's brain, which can cause confusion, agitation and a lack of awareness. Patients may experience headaches, difficulties with written or spoken language, anxiety and occasional seizures.

Neurotoxicity can occur with or without cytokine release syndrome. If a patient also experiences CRS, neurologic symptoms more commonly occur after CRS. It is reversible in most cases, but in rare cases, cerebral oedema associated with neurotoxicity may develop, which is potentially fatal.

Macrophage-Activation Syndrome

The severe inflammation of the immune system, which can cause multi-organ failure.

Febrile Neutropenia

An abnormal decrease in the number of certain white blood cells in the blood coupled with fever.

B Cell Aplasia

Low number of B cells or no B cells.

Anaemia

A condition in which the number of red blood cells is below normal.

Thrombocytopenia

A decrease in the number of platelets in the blood.

Hypogammaglobulinemia

A reduction in all types of gamma globulins, including antibodies that help fight infection.

Severe side effects are often the result of the high activity of the immune system brought on by the CAR-T therapy. Immunosuppressive drugs and corticosteroids are used in symptom management, with the goal of curtailing the side effects without removing the CAR-T cells completely.

It is important patients and caregivers can identify symptoms quickly so they can be treated appropriately, especially since the symptoms of some side effects (like neurotoxicity) are the same as those of other medical conditions which are treated very differently.

Challenges

While the clinical results are compelling, there are several challenges associated with CAR-T therapy.

Varied results

While some patients respond to CAR-T therapy very well and their disease goes into remission, there are still others that don't and it's unknown why. Who is the ideal candidate for CAR-T therapy? Are there genetic or clinical factors make one patient a better candidate than another? Do prior therapies impact results? Are there predictors that can help gauge a patient's response?

Lack of long-term data

CAR-T is a relatively new therapy and early trial findings have been impressive. However, the lack of long-term data leaves us with many unanswered questions. Will the short-term results will hold up over time? What side-effects will patients face in the future? And what are the long-term psychosocial effects of CAR-T and the potential of serious side-effects for patients and caregivers?

Wait time to treatment

As current CAR-T therapy is customized to individual patients, there is a time lapse between when patients are accepted to receive CAR-T until their manufactured T cells are returned for infusion. As patients currently eligible for this treatment are often quite ill, it can be challenging to stop the cancer from advancing and keep the patient healthy enough to receive the therapy during this time span.

Availability

CAR-T therapy can only be administered in specialty cancer centres who have been certified to provide the therapy, which limits its availability. Patients who are eligible for the therapy may have to travel from and stay away from home for several weeks – for blood sampling, during infusion and through the observation period. This can be both disruptive and expensive for patients and carers.

Cost of treatment

There is a significant financial cost associated with CAR-T therapy, both for the therapy and associated medical services. While some manufacturers have created outcome-based pricing arrangements, with the company only receiving payment if the patient responds to the treatment, the cost of CAR-T therapy is significant to payers – public programs, insurance programs and individual patients alike.

Manufacturing issues

There is room for improvement regarding the CAR-T therapy manufacturing process. Failures in the manufacturing process lead to longer times for patients to wait for infusion with a suppressed immune system, which can be fatal.

Glossary

Antigen
A substance that is recognized by the immune system as foreign to the body.

Complete response rate (CR)
The percentage of patients who respond to treatment with the disappearance of all signs of cancer. Even if patients do not achieve CR, they could experience a partial response (PR). Overall response rate (ORR) is the sum of CR and PR.

Cytokines
Proteins secreted from immune cells into the bloodstream that affect many different processes in the body.

DLBCL
Diffused Large B-cell Lymphoma is the most common type of non-Hodgkin lymphoma. It is usually aggressive. DLBCL is marked by rapidly growing tumours in the lymph nodes, spleen, liver, bone marrow or other organs.

Immunotherapy
Therapy that stimulates the immune system to fight disease.

Median overall survival (mOS)
The median length of time from the date of diagnosis or the start of treatment that patients are still alive.

PMBCL
Primary Mediastinal Diffuse Large B-cell Lymphoma is a subtype of diffuse large B-cell lymphoma (DLBCL) that occurs in the thymus gland or lymph nodes in the centre of the chest.

Refractory cancer
Cancer that does not respond to treatment.

T cells
One type of white blood cell that attacks virus-infected cells, foreign cells and cancer cells. They also produce a number of substances that regulate the immune response.

TFL
Transformed follicular lymphoma is when follicular lymphoma (FL) an indolent B-cell lymphoma, changes to be a more aggressive cancer.

Transmembrane proteins
A protein membrane covering the surface of the cell and acts as a gateway that permits certain substances to cross the cell membrane.

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[i] Institute for Clinical and Economic Review. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value, Draft Evidence Report. December 19, 2017.