

CAR T cells: Recent Cell Based Therapy for Cancer



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Introduction

One of the main causes of death in the globe is cancer. Numerous traditional cytotoxic methods for treating neoplastic illnesses have been developed over the years. However, due to their limited efficacy in light of the heterogeneity of cancer cells, there is a continuing quest for therapeutic strategies that provide better results, such as immunotherapy, which makes use of and boosts the immune system's normal functioning (1,2,3).

Certain cancers are treated with chimeric antigen receptor (CAR) T-cell therapy, which modifies T-lymphocytes or T-cells to make them more effective cancer-fighting cells. While long-term data are still being gathered, CAR T-cell therapy is showing to be a very successful method of treating some blood cancers (4). Chimeric antigen receptor (CAR)-T cell therapy is among the newest and most effective treatments for blood cancer. In order to combat cancer, these treatments rely on your body's immune system (5).

CAR T- Therapy

A type of cancer immunotherapy known as CAR T cell therapy uses T cells, which are immune cells, that have been genetically altered in a lab to increase their capacity to recognise and destroy cancer cells (6).

CAR T-cell therapy requires platforms for quick, dependable, and secure gene transfer. Through the use of both viral and non-viral transfection approaches, ex vivo genetic alteration of autologous T-cells isolated during leukapheresis is achieved. Then, modified T-cells are raised in culture (Figure 1). Typically, after the CAR Tcell product has been produced and has passed all quality control testing, the patient will first get lymphodepleting chemotherapy, then receive an infusion of CAR T cells. The first chimeric receptor was developed in 1989 by Eshhar's group at the Weizmann Institute of Science in Israel (7)

CARTs may detect unprocessed antigens as well as glycolipid and carbohydrate structures that are frequently expressed on a tumour cell's cell surface and work as treatment of cancer.

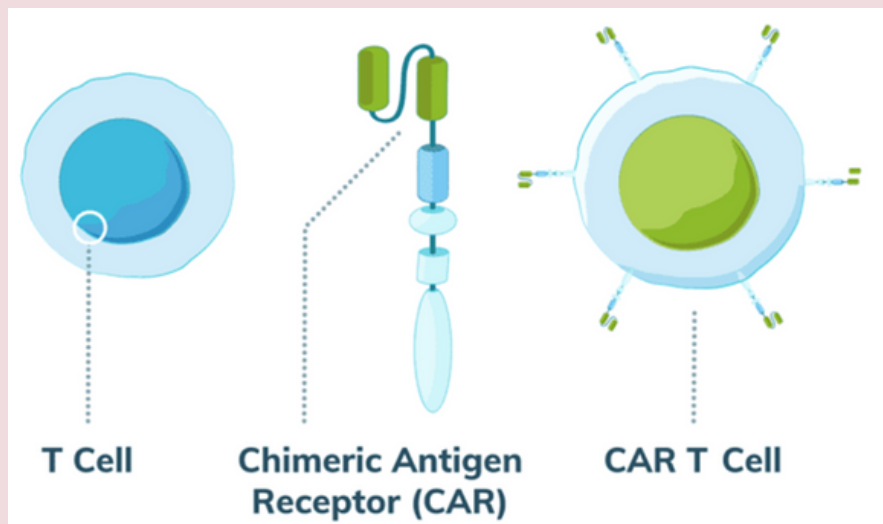


Figure 1: CAR T cell preparation

Specific cells and organs that make up the immune system guard the body against disease and cancer. These include T lymphocytes, which look for and eliminate aberrant cells, including cancer cells. The immune system needs to be retrained to recognize and kill cancer cells since cancer cells can occasionally find ways to elude it. One cutting-edge method for training the immune system to combat cancer is CAR T-cell therapy (8).

After a blood sample of a patient's T cells is taken, the cells are altered to generate distinctive structures termed chimeric antigen receptors (CARs) on their surface. The receptors on these CAR T cells may help the T cells when they are reinjected into the patient find and fight cancer cells throughout the body (9).

CAR T Therapy Process

In this process following methods are included (10) (Figure 2):

1. T cells from a patient are taken. T cells are collected via the apheresis technique, which involves drawing blood from the body and separating one or more blood components (such as platelets, plasma, or white blood cells). The remaining blood is subsequently given to the body.
2. In a lab, T cells are redesigned. The T cells are delivered to a lab or a medicine production facility where they are genetically modified by injecting DNA into them, resulting in the production of chimeric antigen receptors (CARs) on the cell surface.
3. The reengineered T cells are now referred to as "chimeric antigen receptor (CAR) T cells." Proteins called CARs enable T lymphocytes to detect an antigen on certain tumour cells.
4. The CAR T cells are then multiplied. The quantity of the patient's genetically altered T cells is "expanded" through laboratory cell growth. Once there are sufficient CAR T cells, they are frozen and sent to the hospital or facility where the patient is being treated.
5. The CAR T cells are defrosted and administered to the patient after being thawed at the hospital or treatment facility. Before receiving an infusion of CAR T cells, a lot of patients undergo a brief course of one or more chemotherapy drugs, referred to as "lymphodepletion." The patient's circulation begins to multiply with the reintroduction of 1. CAR T cells. These cells are known as "attacker" cells because they are capable of identifying and attacking cells that have the specific antigen on their surface.

6. In order to prevent recurrence, the CAR T cells might be useful. Even if the CAR T cells are given months after the injection, they may still be present in the body and eliminate all cancer cells. Some blood cancer types have seen long-term remissions as a result of the treatment.

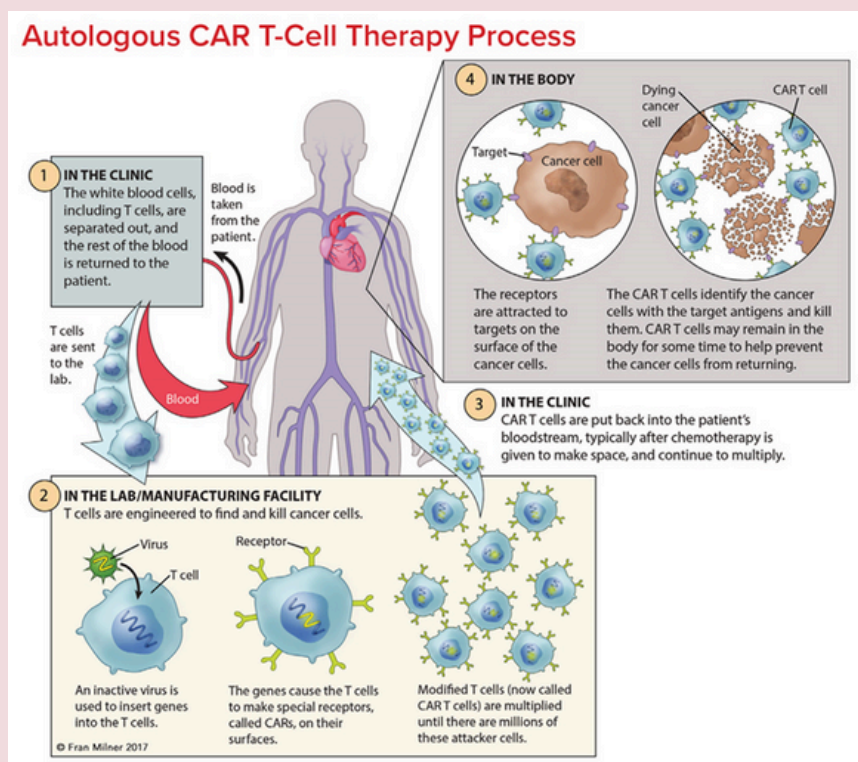


Figure 2: CAR T cell therapy process

Side Effects

Dysregulation of Cytokine Release (CRS). The use of CAR T cells is frequently associated with this potentially serious side effect. Cytokines, which aid T cells in carrying out their duties, are produced when CAR T cells multiply in the body and eliminate cancer cells.. From minor flu-like symptoms, which may include (5,9):

- Fatigue
- Nausea
- Fever
- Chills

The symptoms of CRS are:

- Cardiac Arrest
- Cardiac Arrhythmia
- Hemophagocyticlymphohistiocytosis
- Low blood pressure
- Multiple Organ Failure
- Poor lung oxygenation

Biological Toxicities. Neurological side effects vary amongst CAR-T products in terms of frequency, severity, and origin. Language difficulty (aphasia), confusion, delirium, involuntary muscle twitching, hallucinations, or indifference are typical symptoms. Also mentioned are seizures.

Off-tumor, On-target Toxicity The selection of the appropriate tumor-associated antigen to target is crucial for the safe and effective usage of CAR T cells. Sadly, it is uncommon to locate such a perfect target. Numerous tumour antigens are additionally expressed on healthy tissue cells. Especially when cells in vital tissues like the heart, lung, or liver display the target antigen, damage to such non-cancerous normal tissue by CAR T cells may be fatal.

Anaphylaxis (Life-threatening Allergic Reaction) (Life-threatening Allergic Reaction). An extreme immunological reaction against the CAR itself, known as "anaphylaxis," has the potential to occur in a patient getting CAR T-cell treatment. Hives, swelling of the face, low blood pressure, and breathing difficulties are all signs of anaphylaxis. Few cases of acute anaphylaxis have been reported. For patients receiving CAR T-cell therapy, careful observation and prompt treatment of this life-threatening adverse event are essential.

Tumor Lysis Syndrome (TLS). Tumor lysis syndrome (TLS), a collection of metabolic issues that can arise as a result of the breakdown of dying cells—typically at the start of hazardous cancer treatments—is another well-known adverse effect of CAR T-cell therapy. After CAR T-cell therapy, TLS can, however, be postponed and may come around a month or more later. TLS is a potentially fatal side effect of any therapy that destroys cancer cells, including CAR T cells. It can harm organs and damage surrounding tissue. Through routine supportive care, the complication has been controlled.

Future of CAR T Therapy

Studies of CAR T-cell treatment in multiple myeloma and other blood malignancies, such as chronic lymphocytic leukaemia (CLL), also show promise. Additionally, studies investigating the use of CAR T-cell therapy in the management of solid tumours are also being conducted (3).

The majority of patients taking part in CAR T-cell trials have only been monitored for a brief period of time, but data revealing early therapeutic responses is quickly surfacing. Following a thorough analysis of trial participants' long-term behaviour, researchers will be able to forecast how long these responses will last. Clinical trials should enrol more children and adults, for many reasons. Researchers will be better able to comprehend the consequences of this kind of medication, find strategies to lessen its toxicity, and enhance the management of negative side effects with larger study populations that are assessed over longer time periods (3)

References

1. PricemanSJ, Forman SJ, Brown CE. Smart CARs engineered for cancer immunotherapy. *Curr Opin Oncol.* 2015; 27(6): 466- 474
2. Chmielewski M, Hombach AA, AbkenH. Antigen-specific Tcell activation independently of the MHC: Chimeric antigen receptor-redirected T cells. *Front Immunol.* 2013; 4: 371
3. Zhang C, Liu J, Zhong JF, Zhang X. Engineering CAR-T cells. *Biomarker Res.* 2017; 5: 22.
4. Park HJ, Kusnadi A, Lee EJ, Kim WW, Cho BC, Lee IJ, Seong J, Ha SJ. Tumor-infiltrating regulatory T cells delineated by upregulation of PD-1 and inhibitory receptors. *Cellul Immunol.*2012; 278(1-2): 76-83.
5. Sadelain M, Brentjens R, RiviereL. The basic principles of chimeric antigen receptor design. *Cancer Discov.* 2013; 3(4): 388- 398.
6. Haji-Fatahalih M, Hosseini M, Akbarian A, Sadreddini S, Jadidi-Niaragh F, YousefiM. CAR-modified T-cell therapy for cancer: An updated review. *Artificial Cells, NanomedBiotechnol.* 2016; 44(6): 1339-1349.
7. AbkenH. Driving CARs on the highway to solid cancer: some considerations on the adoptive therapy with CAR T cells. *Hum Gene Ther.* 2017;28(9):1047-1060.
8. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: Recognition and management. *Blood.* 2016; 127(26): 3321-3230.
9. Johnson LA, June, C.H. Driving gene-engineered T cell immunotherapy of cancer. *Cell Res.* 2017; 27(1): 38-58.
10. Davila ML, Brentjens RJ. CD19-Targeted CAR T cells as novel cancer immunotherapy for relapsed or refractory B-cell acute lymphoblastic leukemia. *Clin Adv Hematol Oncol.* 2016; 14(10): 802-808