

The Promise of CAR T Cell Therapy



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The novel therapy of CAR T cells (Chimeric Antigen Receptor T cells) has been gaining much recognition in treating cancer along with or as an alternative to chemotherapy. They are T cells engineered with chimeric receptor proteins that increase the specificity to target a particular antigen. This artificial T cell receptor is widely used as a part of immunotherapy.

The term chimeric is used because these are the fusion proteins that are made by joining two genes that originally coded for separate proteins i.e., antigen-binding gene and T cell activating function of a gene into a single receptor. CAR T cells specifically identify cancer cells and destroy them by interacting with the Tumor-Associated Antigens (TAAs) expressed on the tumor cell surface. CAR specifically binds with TAAs then T cells get activated through the phosphorylation of immune receptor tyrosine-based activation motifs (ITAMs).[1] This consequently induces T cell proliferation, cytokine secretion, and cytotoxicity. With guidance from their engineered receptor, CAR T cells multiply in the patient's body and, recognize and kill any cancer cells that harbor the target antigen on their surfaces.

CARs comprise three parts:

1. An extracellular antigen recognition domain of the single-chain Fragment variant (scFv) obtained from an antibody, the Ectodomain
2. An anchor to the T cell membrane, the Transmembrane domain
3. An intracellular T cell activation domain of CD3 ζ , the Endodomain

Each CAR bridges the cell membrane. Part of the receptor is located outside the cell and part is within the cell. The area of the CAR that protrudes out from the cell's surface is composed of fragments, or domains, of artificially designed antibodies. The internal part of each CAR is composed of signaling and 'co-stimulatory' domains. These transmit signals into the cell after the interaction of receptor and antigen. The different domains that are used can affect the cells' overall function. [2]

CAR T cells can be either derived from T cells in a patient's blood (autologous treatment) or derived from the T cells of another healthy donor (allogeneic i.e., HLA-identical donors).

Allogeneic CAR T cells therapy has moved into early-phase clinical testing anticipating that it will offer significant advantages over autologous regimens. Although there are three FDA-approved autologous CAR T-cell products, there are no allogeneic CAR T-cell products in the market. [3] The basic steps of CAR T cells production include:

1. T cells isolated from blood (autologous or allogenic)
2. A new gene that codes for chimeric antigen receptor is integrated into the T cells
3. Engineered T cells become specific to the desired target antigen
4. Tissue culture of these engineered T cells done for expansion
5. Infusion of engineered T cells into the patient [4]

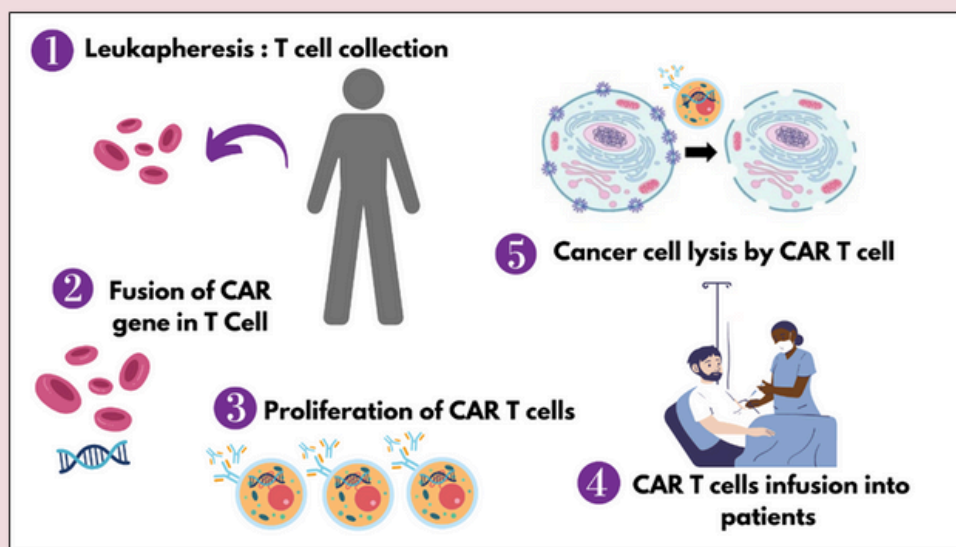


Fig. 1: Preparation of CAR T-cells for cancer treatment

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Side effects of CAR T cell therapy

1. Cytokine release syndrome (CRS)- results from the overproduction of inflammatory cytokines like tumor necrosis factor-alpha (TNF- α) and interleukin 6 (IL-6).
2. CAR T-cell-related encephalopathy syndrome (CRES)- Symptoms of CRES include mild confusion, disorientation, fatal cerebral edema, and speech difficulties.
3. Immune effector cell-associated neurotoxicity syndrome (ICANS)- ICANS includes CRES and other neurological toxicities arising from CAR T and other therapies. Symptoms may include seizures and loss of balance.
4. On-target/off-target toxicity- Occurs when CAR T-cells attack non-tumor cells expressing the target antigen. These therapies target cancer cells and reduce the number of healthy antibody-producing B cells, thereby the patient is more susceptible to infection.

5. Allergic reactions during the infusion- A weakened immune system, with an increased risk of serious infections. Low blood cell counts, can increase the risk of infections, fatigue, and bruising or bleeding. [5]

6. Tumour Lysis Syndrome (TLS)- a group of metabolic complications that can occur due to the breakdown of dying cells which can cause organ damage and breakdown of CAR T cells. [6]

7. FDA-approved CAR T cell therapies

i. Abecma (Idecabtagene vicleucel)

Abecma is used to cure Multiple myeloma. B- Cell Maturation Antigen (BCMA), is expressed on the surface of both normal and malignant plasma cells implicated in multiple myeloma. Overexpression of this antigen promotes the growth of myeloma cells and cell proliferation and survival. Idecabtagene vicleucel (Abecma) is the first CAR T-cell therapy that targets BCMA. The antigen-specific activation of Abecma results in CAR T-cell proliferation, cytokine secretion as well as subsequent death of BCMA-expressing cells. [7]

ii. Kymriah (Tisagenlecleucel)

This therapy is used in the treatment of Acute Lymphoblastic Leukemia. Kymriah is genetically-modified, and CD19-directed autologous immunotherapy. The patient's T cells are programmed with a transgene which encodes a CAR to target CD19. It includes a murine single-chain antibody variable fragment which recognizes CD19, which in turn is fused to intracellular signaling domains from 4-1BB (CD137) and CD3 ζ . The intercellular signaling domain CD3 ζ initiates antitumor activity and T-cell activation. 4-1BB plays a role in enhancing the expansion and persistence of the CAR cells. The CAR binds to the CD19-positive cells and sends a signal to begin T-cell activation, expansion, and targeting T-cell elimination, thereby increasing the persistence of Tisagenlecleucel cells due to the property of individual components present in therapy. [8]

iii. Tecartus (Brexucabtagene autoleucel)

This combats Mantle Cell Lymphoma. It consists of two intracellular CD28/CD3 domains: CD3 ζ is a signalling domain, and CD28 is a costimulatory domain. It also has an exterior domain with a single-chain variable segment connected to the transmembrane domain by a hinge. It is introduced into T cells using a gamma-retrovirus vector. After attaching to the CD19 receptor on lymphoma cells, CAR-T cells activate T cells by stimulating signalling pathways through the CD3 ζ domain. Granzyme B and perforin are immediately released by CAR-T cells, which promotes the killing of tumors and mediates lymphoma apoptosis.[9]

iv. Breyanzi (Lisocabtagene maraleucel)

Breyanzi targets B-lymphocyte surface antigen B4 and is employed in the treatment of B-cell Lymphoma. This CAR constitutes CD28 transmembrane domain, 4-1BB costimulatory domain, and CD3 ζ activation domain. The transmembrane domain is responsible for the tolerance or activity of T cells. The costimulatory domain controls interferon production and cytotoxic T-cell activity. The activation domain carries out the activation of T cells via CD2, which is a T cell surface adhesion molecule. [10]

v. Yescarta (Axicabtagene ciloleucel)

This therapy treats Follicular Lymphoma. Yescarta, which is a CD19-directed genetically modified autologous T-cell immunotherapy, binds to both, CD19-expressing cancer cells as well as normal B cells. Activation of downstream signaling cascades occurs, leading to T cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines after the engagement of anti-CD19 CAR T cell with CD19-expressing target cells, the CD28 and CD3-zeta costimulatory domains. The consequence of this is the killing of CD19-expressing cells. [11]

Scope in India

On the 4th of June 2021, the IIT Bombay team and cancer care in India carried out the first CAR-T cell therapy (a type of gene therapy) at the Bone Marrow Transplant unit at ACTREC. This gene treatment is undergoing early-stage pilot clinical studies and is a "first in India." For the purpose of performing a first-in-human phase-1/2 clinical study of the CAR-T cells, the team has been granted 19.15 crore by the National Biopharma Mission-BIRAC of the central government. The Bioscience and Bioengineering (BSBE) department of IIT Bombay, led by Prof. Rahul Purwar, created the revolutionary CAR-T cells that will serve as medications.

National Biopharma Mission has invested in the development of a Lentiviral vector manufacturing facility for packaging plasmids. The transformed T cell is then transferred into the body using this packaged plasmid. It is included in the expansion of the cGMP facility utilised for CAR T-cell production and T-cell transduction. Additionally, this was given to two other charities. The Department of Biotechnology supports the development of CAR-T cell technology for diseases like acute lymphocytic leukaemia, multiple myeloma, glioblastoma, hepatocellular carcinoma, and type-2 diabetes.

Each patient's CAR-T cell therapy costs approximately 3-4 crore (INR). The major concern is to develop this technology in a cost-effective manner so that it can be made available to a large number of patients. If the trials are successful, it may save millions of lives by making the treatment available in India at an affordable cost. [12]

The estimated market size for CAR T cell therapies in India is 20000 to 40000 patients with leukemia and lymphoma per year. Kiran Mazumdar- Shaw, Biocon founder, and managing director believes the production schedule including cell manipulation should be hospital-based unlike that in the US where a central accredited location far from the medical center is chosen. This allows earlier intervention in the patient's course of treatment and hence, increases the therapy's chances of success. [13]

Due to the limitations associated with autologous therapy, Allogeneic CAR T cell therapy is explored. Extensive manufacturing time and effort for developing personalized CAR T treatments accompanied by customization to that particular patient are significant drawbacks. As a consequence of personalized manufacturing, the prices of these therapies are exorbitantly high. However, allogeneic therapy also tends to demonstrate potential drawbacks. As they're derived from a donor, they require compatibility testing with the patient, similar to the organ transplant process. Hence they are also prone to rejection if they are not compatible. [14]

The future prospects to optimize the design and delivery of CAR T cells seems hopeful. Though it has innumerable benefits, there are a few drawbacks that need to be overcome. CAR T cells for the time being have not proven effective for a majority of people with blood cancer, due to toxicity issues or high expenses. To incorporate CAR T cells against other diseases, strategies are being developed to avoid antigen-negative relapse, control toxicity, and increase efficacy and persistence. [15]

References

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Fun & frolic - Crossword | solution

Created using the Crossword Maker on TheTeachersCorner.net

Across

5. Immortalized cell line (ctx) **(yescarta)**
6. Cell-based therapy to treat Type 2 diabetes (**apligraf**)
7. Dermal fibroblasts for wound repair from Arita Medical (**recell**)
8. CAR-T therapies for the treatment of relapsed or refractory large B-cell lymphoma, (**yescarta**)

Down

1. CAR-T therapy for the treatment of acute lymphoblastic leukemia (**kymriah**)
2. Approved in vivo gene therapy (**glybera**)
3. World’s first ‘personalized’ cancer therapy marketed by Dendreo (**sipuleucel**)
4. Abbreviated Michigan Cancer Foundation Breast Cancer Cell Lines (**mcf**)
9. Chimeric antigen receptor T-cell therapy (**cart**)