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Review Article

Chimeric Antigen Receptor T-cell Therapy (CAR T)

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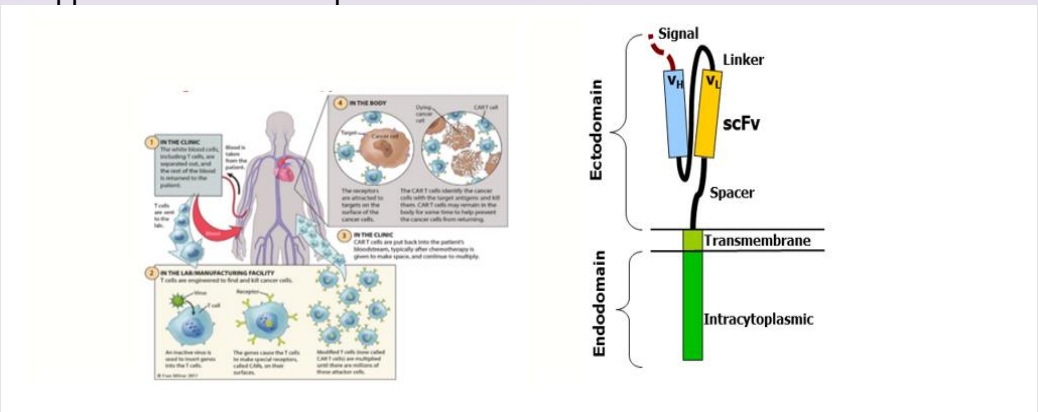
Introduction

This is an adoptive T-cell therapy which uses engineered T-cell. In which they are obtain from a patient's immune system by its own to attack cancer cells through targeting proteins expressed on the cellular membrane, that process involves obtaining T-cells via a leukapheresis procedure. These cells are sent to a centralized manufacturing facility where they are genetically modified to produce specific chimeric antigen receptors and expanded in a cell culture. This process may take up to few weeks. This product is then returned to the treating facility and re-infused into the patient recovery. **(Srivastava & Riddell, 2018)** Chimeric antigen receptor T-cell therapy is used to treat certain blood cancers, and still being studied in the treatment of other types of cancer. This is also called as CAR-T Immunotherapy. The first CAR T cell therapy was approved by FDA in 2017, and there are now 6 approved CAR T therapies.



Chimeric antigen receptor structure-Chimeric antigen receptors are composed of four regions

- Antigen recognition domain
- Extracellular hinge region
- Transmembrane domain
- Intracellular T cell signalling domain.

Chimeric antigen receptors combine many facets of normal T cell activates a link between an extracellular antigen recognition domain to an intracellular signalling domain.

Immunotherapy

Immune cells or antibodies can be produced in the laboratory under tightly controlled conditions and then given to patients for the treatment of cancer.
Lymphocytes, a subtype of white blood cells- There are three types of lymphocytes

1. B lymphocytes (B cells) -for fight infection.
2. T lymphocytes (T cells) -including helping B lymphocytes to make antibodies to fight infection, and directly killing infected cells in the body.
3. Natural killer cells - attack infected cells and eliminate viruses.

- For treatment that utilizes the body's own immune system to fight cancer.
- This improves the body's ability to detect and kill cancer cells.
- This involves immune cells or antibodies can recognize and kill cancer cells.

Chimeric antigen receptors are the receptor proteins that have been engineered to give new ability to target a specific antigen to the T cells. The receptors are chimeric because they have ability to combine with both antigen-binding and T cell activating functions into a single receptor.

Procedure for CAR-T Cells Development: -

CAR T-cells are generally produced within 10 days to three weeks of the ex vivo culture. Mfg. of CAR T-cells as investigators seeks to encode CARs into T-cells that preserve the functional capacity of T memory stem cells.

- T cells are reengineered in a laboratory, T cells are sent to a lab. or a drug mfg. facility for the modify to genetically engineered, to produce chimeric antigen receptors on the surface of the cells.
- After that, the T cells are known as "chimeric antigen receptor (CAR) T cells." that allows the T cells to recognize an antigen on targeted tumor cells.
- The reengineered CAR T cells are then multiplied, at the research center, the CAR T cells are thawed and then infused into the patient. Many patients are given a brief course of one or more chemotherapy agents, called "lymphodepletion," where the "attacker" cells that will recognize, and attack, cells that have the targeted antigen on their surface.
- The CAR T cells may help guard against recurrence. CAR T cells may eradicate all of the cancer cells and may remain in the body months after the infusion; the therapy has resulted in long-term remissions for some types of blood cancer.

- After the infusion of CAR T cells into a patient, they act as a "living drug" against cancer cells. When contact with their targeted antigen on a cell, CAR T cells bind to particular target and become activated then proliferate and become cytotoxic.

- CAR T cells destroy cells through stimulated cell proliferation, cytotoxicity and by causing the increased secretion of factors which affect other cells such as cytokines, interleukins and growth factors.

❖ Contraindications

The following are considered contraindications to CAR T-cell therapy regardless of the product: -

- Pregnancy
- Members receiving immunosuppressive therapy for an autoimmune disorder.
- Any active, uncontrolled infection.
- Uncontrolled Human Immunodeficiency Virus (HIV) infection.
- Active hepatitis B or hepatitis C infection for lymphomas.
- Active hepatitis B or hepatitis C or CMV infection for multiple myeloma.
- Hepatitis B or C infection.
- Active graft vs. host disease in members with a history of allogeneic hematopoietic stem cell transplant.
- Primary central nervous system lymphoma.
- Solid tumors.

FDA approved T-cell (CAR) therapies: -

Generic Name	Brand Name	Target Antigen	Targeted Disease
Tisagenlecleucel	Kymriah	CD19	B-cell acute lymphoblastic leukemia (ALL)
			B-cell non-Hodgkin lymphoma (NHL)
Axicabtagene ciloleucel	Yescarta	CD19	B-cell non-Hodgkin lymphoma (NHL)
			Follicular lymphoma
Brexucabtagene autoleucel	Tecartus	CD19	Mantle cell lymphoma (MCL)
			B-cell acute lymphoblastic leukemia (ALL)
Lisocabtagene maraleucel	Breyanzi	CD19	B-cell non-Hodgkin lymphoma (NHL)
Idecabtagene vicleucel	Abecma	BCMA	Multiple myeloma
Ciltacabtagene autoleucel	Carvykti	BCMA	Multiple myeloma

Clinical Evaluation of CAR T Immunotherapy for Solid Tumor Markers: -

CAR T-cells have been evaluated for the treatment of a various solid tumors. The proportions of patient's response with a measurable objective in these trials are variable, major hurdle in implementing CAR T-cell therapy against solid tumors is target selection. CAR molecule can engage in two separate TAAs (tumor-associated antigens) can also be used to overcome antigen escape. CAR T-cells targeting fibroblast activation protein (FAP- alpha) which is expressed on the surface of cancer associated fibroblasts have shown efficacy in controlling tumor growth. FAP+ stromal cells also play important roles in the periphery, off-tumor targeting of these populations by CAR T-cells results in cachexia and hematological toxicities in murine models, raising potential concern over FAP as a target. The CAR T-cell therapy is emerging as a powerful therapy to be incorporated into mainstream oncologic treatment very soon, the optimal conditioning for CAR T-cell therapy to delineate optimal combinatorial strategies to improve the therapeutic potential of CAR T-cells. This identifies the active "ingredients" of the CAR T-cell product. Thus, T cell therapy undoubtedly marks a new era in cancer and the beginning of personalized cell therapy with targeted specifications.

Various side effects of CAR T-cell therapies: -

1. CAR T-cell therapies can cause severe side effects like other cancer therapy, One of the most frequent and serious side effects is cytokine release syndrome (CRS).
2. It can also cause dangerously high fevers and precipitous drops in blood pressure, in some cases, severe CRS can be fatal.
3. The other side effects of particular concern with these therapies are neurologic effects, including severe confusion, seizure-like activity, and impaired speech.
4. **Macrophage Activation Syndrome (MAS),** this one is closely associated with severe CRS. It is a condition caused by the excessive activation and multiplication of T cells and macrophages.
5. **Tumor Lysis Syndrome (TLS) is the** side effect of CAR T-cell therapy in which a group of metabolic complications can occur due to the breakdown of dying cells at the onset of toxic cancer treatments.
6. CAR T-cell therapy targeting antigens found on the surface of B cells not only destroys cancerous B cells along with normal B cells that cause **B-Cell Aplasia.**
7. Other general side effects can include:
    - Tremors, Headaches, Loss of balance, Trouble speaking, Seizures.

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