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A Brief Review on CAR-T Cell Therapy

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ABSTRACT

Cancer is one of the leading causes of death worldwide. Chimeric antigen receptor-T cell therapy is an immunotherapy treatment that uses a patient's immune system to fight cancer. CAR-T therapy entails removing T cells from a patient's blood via Leukapheresis and genetically modifying them in-vitro to express the chimeric antigen receptor. These modified T cells are then reinfused into the patient, where they recognize the tumor-specific antigen and produce anti-tumor activity. This cytotoxic effect can also cause toxic effects such as cytokine release syndrome, neurotoxicity, and off-tumor toxicity, all of which can be fatal and necessitate ongoing management. More research and development are needed to improve anti-cancer efficacy. This review discusses the structure of chimeric antigen receptors, the production of chimeric antigen receptor-T cells, major side effects, and how to manage them.

1. INTRODUCTION

Cancer is the malignant growth resulting from uncontrollable cell division and potentially invades other parts of the body. According to the world health organization (WHO), 18 million new cases of cancer are diagnosed every year, and is the second worldwide cause of death about 8.8 million deaths in a year(1). Treatment for cancer includes chemotherapy, radiotherapy, immunotherapy, and surgical treatment. Chimeric antigen receptor T cell (CAR-T) therapy is a type of Immunotherapy that utilizes the body's immune system to fight against cancer and improve the body's ability to detect and kill cancer cells.

T cells are the vital part of the immune system that recognizes abnormal cells in the body. Cancer has developed mechanisms to evade killing by T cells. CAR-T therapy involves T cells that have been genetically engineered to enable the T cells to recognize cancerous cells. The receptors are chimeric because they combine both antigen binding and T cell activating functions into a single receptor.

Structure of Chimeric antigen receptor (CAR)

The structure of CAR consists of an antigen domain, hinge, one or more costimulatory domains, and main signaling domain. The first generation CARs have the main signaling domain whereas second and third-generation CARs include one or two co-stimulatory domains along with the main signaling domain, respectively. Second and third-generation CAR-T cells are more potent (2).

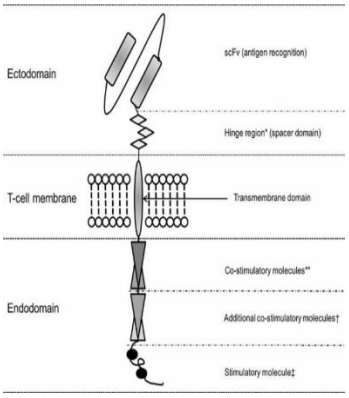

Figure No. 1: Basic structure of chimeric antigen receptor (2)

2. Main text

2.1. Production of CAR T cells

The first step in the production of CAR T cells involves isolation of T cells through a process called Leukapheresis, where white blood cells are isolated from either patient's blood (autologous) or a healthy donor (allogenic) (3). These T cells are taken to the lab and are activated using anti-CD3 (cluster differentiation 3) or anti-CD3/anti-CD28 monoclonal antibody-coated beads and are later genetically modified by transduction with viral vector to express CAR (4)(5). The virus used is inactive and are not able to replicate or cause any disease and the viral vector can be lentiviral which delivers gene construct to non-dividing cells or retroviral that delivers gene construct to dividing cells (2).

These modified T cells are then grown and expanded and are reinfused into the patient. Before infusion, the patient is treated with chemotherapy for lymphodepletion i.e., to prepare for the reception of CAR T cells, as the CAR T cells may not persist for a longer time and may have decreased efficacy if not treated with chemotherapy (4).

Persistence can be vital in the case of Acute lymphoblastic leukemia (ALL) whereas it may not be necessarily important in Non-Hodgkin's lymphoma (NHL) (4)(6). Three factors have an impact on CAR T cell proliferation and persistence, they are lymphodepletion regimen, the quantity of CAR T cells, and cell product composition. Homogenization of cell product composition can be done by 1:1 ratio $CD4^+/CD8^+$ (7).

2.2. Toxicities of CAR T cell therapy and their management

Though CAR T cell therapy has promising antitumor effects it has many adverse effects.

2.2.1. Cytokine Release Syndrome (CRS)

It is the common side effect that occurred due to over activation of the immune system and release of cytokines (8)(9). These cytokines activate other cells of the immune system especially leading to elevation of interleukin-6 (IL-6) (6). The first stage of CRS includes signs of flu, muscle aches, and the patient can develop tachycardia, respiratory distress, and arrhythmias, severe hemophagocytic lymphohistiocytosis (HLH). The severity of CRS depends on the number of cells infused, degree of in-vitro CAR T cell proliferation, and patients with comorbidities, those who develop early onset of CRS within 3 days of CAR-T

cells infusion (10)(11). CRS after CAR-T cell therapy can occur in 54-91% of patients and severe CRS in 8-43% (12)(13).

Only the patients with limited comorbidities and who can tolerate severe CRS should be infused with CAR-T cell therapy (12).when an infection is suspected, patients should be assessed using blood, urine cultures, and other tests like CT scan of the chest, respiratory viral screening should be done. The infusion of CAR-T cells is carried out only when the infection has been controlled or ruled out (11).

After infusion of CAR-T cells, patients should be monitored continuously and vital signs are checked every 4 hours. If a patient experiencing a persistent heart rate of 115 beats per minute, vital signs are checked every 2 hours (9). Daily review of metabolic profiles, complete blood count, serum C-reactive protein (CRP) and ferritin levels should be done (11). Management of acute symptoms of CRS can be done through a grading system to assess the severity and provide treatment accordingly (14). Fever can be managed by acetaminophen and hypotension by vasopressors like norepinephrine (9).

Tocilizumab and siltuximab are IL-6 antagonists used as off-label drugs for the reversal of CRS symptoms (11)(6). Tocilizumab is the most commonly used and is effective for treating severe to life-threatening CRS (14) when the condition of the patient is not stabilized after use of tocilizumab then immunosuppressive agents like corticosteroids are considered. Corticosteroids can have an adverse effect on the antitumor activity of adaptively transferred T cells (14)(15).

2.2.2. Neurotoxicity

It involves CAR-T cell-related encephalopathy syndrome (CRES) with symptoms of cognitive disorders, confusion, restlessness, anxiety, aphasia, seizures, delirium, and can develop to fatal cerebral edema. The incidence of neurotoxicity in CAR-T cell-treated patients can be 40% (12). This toxicity is due to systemic cytokines that cross the blood-brain barrier (BBB). CAR-T cells are found in cerebrospinal fluid (CSF) of patients and an increase in CAR-T cell infiltration in CSF is seen due to the release of IL-6 during CRS and hyperthermia (16).

Continuous monitoring of patient given with CAR-T cell therapy through neuroimaging involving MRI, CT, EEG, to determine the severity and funduscopic examination to assess for papilledema. CRES with concurrent CRS can be treated with IL-6 antagonists whereas

corticosteroids are preferred for severe CRES (11) (14) Convulsive and non-convulsive status epilepticus are treated with benzodiazepines and other antiepileptics especially levetiracetam (11).

2.2.3. On-target on-tumor toxicity is due to the rapid destruction of a large tumor mass and massive release of tumor cell components into the circulation causing electrolyte and metabolic disturbances. This type of toxicity is seen in leukemia treatment and the risk is less in treatment to solid tumors (8).

2.2.4. On target off-tumor toxicity, most of the targets of CAR-T cells are also expressed in normal tissues, resulting in engagement of target antigen on non-pathogenic tissue leading to on-target off-tumor toxicity (17)(18). This type of toxicity is majorly seen in solid tumors compared to leukemia and lymphoma (12). A fatal example of On target off-tumor toxicity where a patient treated with CAR-T cells for cancer associated with antigen HER-2/neu has developed respiratory failure and multi-organ dysfunctions leading to death due to reactivity against HER-2/neu expressed on pulmonary tissue (17)(19).

2.2.5. Off-target off-tumor toxicity is the inflammatory reaction beyond the targeted tumor tissue. It is mediated through the CAR-T cell independently of target engagement (12).

2.3 Some Advancements in CAR-T cell therapy for limiting toxicity

2.3.1. Transduction of CAR-T cells with inducible caspase-9 suicide gene that will switch off CAR-T cell proliferation in severe toxicity through gene expression and triggering apoptosis (2)(20).

2.3.2. Bispecific CAR is a bispecific receptor containing two distinct intracellular signaling domains that are expressed as two different CARs on a single cell surface (21).

2.3.3. Tandem CARs are chimeric antigen receptors where two particular antigen recognition sites are joined by a linker and placed in tandem on a single intracellular domain and expressed as a single CAR on a cell surface (21). Bispecific targeting can reduce antigen escape mechanisms(22).

2.3.4. Inhibitory CARs (iCARs) are antigen-specific inhibitory chimeric antigen receptors intended to control T cell responses (23). Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)- and programmed cell death protein 1 (PD-1)- based iCARs can limit cytotoxicity and cytokine secretion induced by chimeric receptor activation (23).

CONCLUSION

CAR-T cell therapy has revolutionized the immunotherapeutic treatment of cancer and has a promising future. However, it can cause many toxic effects which require continuous monitoring and supplement treatments. Advancements in CAR designs and further developments in managing toxicities can enhance the anti-tumor efficacy of the therapy.

List of abbreviations

ALL	Acute lymphoblastic leukemia
BBB	Blood-brain barrier
CAR-T therapy	Chimeric antigen receptor-T cell therapy
CD3	Cluster differentiation 3
CRES	CAR-T cell-related encephalopathy syndrome
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTLA-4	Cytotoxic-T lymphocyte-associated antigen 4
EEG	Electroencephalogram
HLH	Hemophagocytic lymphohistiocytosis
IL-6	Interleukin-6
iCAR	Inhibitory chimeric antigen receptor
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin lymphoma
PD-1	Programmed cell death protein-1
WHO	World health organization

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