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Review on Car-T Cell Therapy for Cancer Treatment

Ms.Shubhangi Bajirao Suryawanshi*,Mr.Rahul D Khaire
PRES College Of Pharmacy, Chincholi, Nashik-422102, Maharashtra, India

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ABSTRACT
A set of illnesses known as cancer involve abnormal cell proliferation and have the ability to invade or spread to different bodily regions. These stand in contrast to benign tumours, which remain stationary. A lump, unusual bleeding, a persistent cough, unexplained weight loss, and a change in bowel habits are all potential warning signs and symptoms.Chimeric antigen receptors (CARs), often referred to as chimeric immunoreceptors or artificial T cell receptors, are receptor proteins that have been modified so that T cells now have the ability to target a particular antigen. Because they integrate antigen-binding and T cell activation functions into a single receptor, the receptors are chimeric. CAR T cell treatment is a form of treatment in which the patient's immune cells, called T cells, are altered in a lab so that they will adhere to and kill cancer cells. An apheresis machine receives blood from a vein in the patient's arm through a tube, filters out all white blood cells—including T cells—and returns the remaining blood back to the patient.
The T cells are then genetically modified in the lab to contain the gene for a unique receptor known as a chimeric antigen receptor (CAR). The CAR T cel ls are multiplied in a lab before being infused into t he patient in large numbers. In order to destroy can cer cells, the CAR T cells can connect to an antigen on the cancer cells.

Keywords
CAR - Chimeric antigen receptor
TCR – T cell receptor
MHC – Major histocompatibility complex
TAG - Tumor-associated glycoprotein
IL2 – Interleukin 2

I. INTRODUCTION

Therapy with chimeric antigen receptor (CAR)-T cells has been revolutionary since it has led to surprisingly positive and long-lasting therapeutic outcomes. CARs are created synthetic receptors that drive lymphocytes—most often T cells—to identify and destroy cells that are overexpressing a particular target antigen. Strong T cell activation and potent anti-tumor responses are brought about by CAR binding to target antigens produced on the surface of cells, which occurs independently of the MHC receptor. There are significant drawbacks to CAR-T cell therapy, though, that still need to be resolved. These drawbacks include potentially fatal side effects linked to CAR-T cells, a lack of effectiveness against solid tumours, inhibition and resistance in B cell malignancies, antigen emigration, poor persistence, poor trafficking and tumour infiltration, and the immunosuppressive microenvironment.[1,2,3]

Car structure
CARs are modular synthetic receptors that consist of Four main components:

(1)Binding domain-
The part of the CAR that imparts target an tigen specificity is the antigen binding domain. the variable heavy (VH) and light (VL) chains of mon oclonal anti-bodies were used to create the antigen-binding domains. These chains were then joined by a flexible linker to create a single chain variable fr agment[4].

(2) a hinge region-
The extracellular structural area known as the "hinge" or "spacer region" is what extends the b inding units from the transmembrane domain. The antigenbinding domain needs access to the targeted epitope, therefore the hinge contributes to length a nd serves to offer flexibility to overcome steric hin drance. The chosen hinge is significant because var iations in the length and makeup of the hinge regio n can impact flexibility, CAR expression, signallin g, epitope recognition, strength of activation output s, and epitope recognition.[5,6]

(3) a transmembrane Domain-
The transmembrane domain of CARs is pr esumably the region with the least amount of chara cterization. The transmembrane domain's primary j ob is to hold the CAR to the T cell membrane, but t

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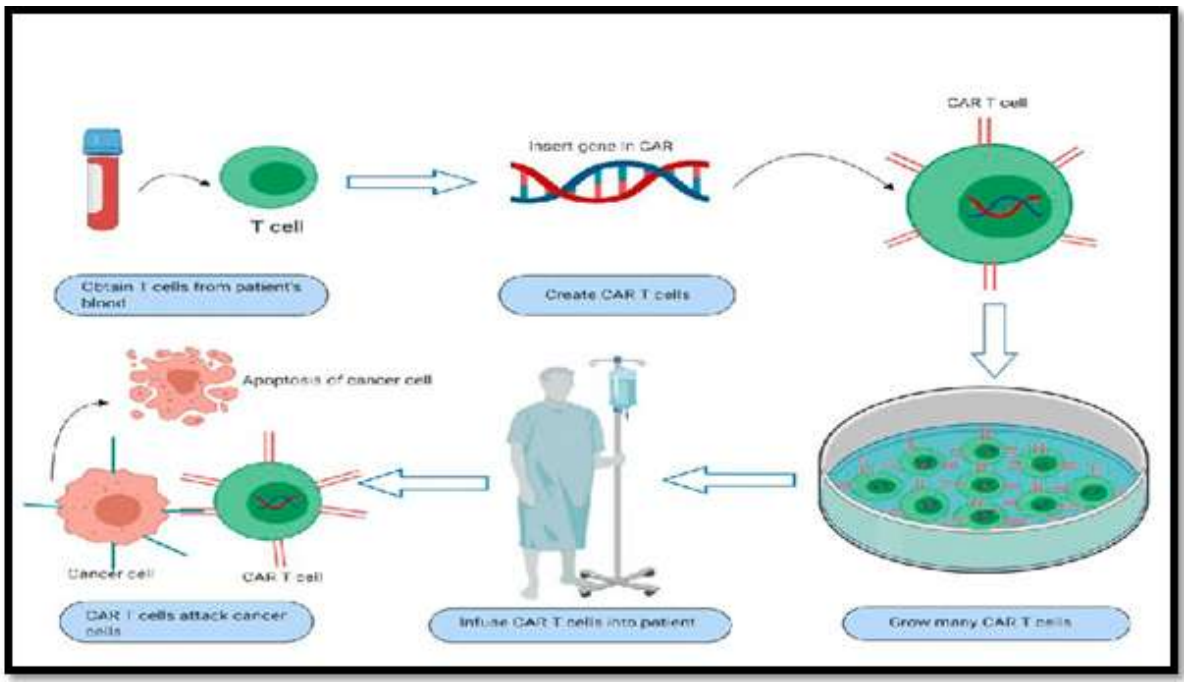
here is evidence that it may also be important for C AR-T cell activity.[7,8]

(4) intracellular signaling-

Understanding the effects of CAR co-stimulation in order to produce CAR constructs with the best endodomain has arguably received the greatest attention in CAR engineering. Second generation CARs were created with one co-stimulatory domain in sequence with the CD3 intracellular signalling domain. The first generation CARs were created in the late 1990s. Third generation CARs did not outperform second generation CARs in models for leukaemia or pancreatic cancer and did not provide any benefits for in vivo treatment.[9,10,11]

Process of car t cell therapy

A molecule called an antigen, which is pre sent on the surface of particular cancer cells, is wha t CAR T
cell therapy instructs T cells to concentrate their att ention toward. To help the T cells acquire this focu s during CAR T cell production, a protein is introd uced to their surface. Chimeric antigen receptors, al so known as CARs, are the name of this protein. A ctually, there are 3 additional proteins in this CAR protein. Two proteins are involved in signalling the T cell to become activated when the first protein bi nds to an antigen on the cancer cell, which is recog nised by one protein on the cancer cell. Adding a C AR to a T cell makes it a "CAR T cell," as the nam e suggests."CAR T cells search for cells that carry t he antigen encoded into the CAR protein, such as s pecific cancer cells, as they float around the body.A CAR T cell becomes activated when it comes into touch with an antigen on a cancer cell. CAR T cells that have been activated proliferate and alert other immune system components to travel to the cancer cell's location. Cytokines are the name given to thes e signalling proteins. Following considerable infla mmation concentrated on the cancer cell brought o n by all of these cytokines and activated T cells, the cancer cell eventually perishes. The cancer may go into remission, which indicates that it has either te mporarily or permanently disappeared, if all of the cancer cells are eliminated.



Process of CAR-T cell therapy

Car t cell therapy for cancer treatment

1.Ovarian cancer

The surprising rate of recurrence of ovarian cancer (OC) following surgery and multi-
agent chemotherapy necessitates the prompt develo pment of novel therapeutic approaches. CAR-Tcell treatment has been used to target tumor associated
glycoprotein 72 (TAG72), which is expressed at a high level on the surface of ovarian cancer.[12]

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2.Breast Cancer

According to studies, HRG1-based CAR-T cells effectively stop the growth of breast cancer cells through the HER family of receptors and can provide a tempting therapeutic strategy to overcome cancer resistance to HER2-based targeted therapy[13].

3.prostate cancer

Targeting chimeric antigen receptors to achieve the desired treatment effects in prostate cancer generally involves using prostate stem cell antigen and prostate-specific membrane antigen[14].

4.Renal cancer

Various forms of renal malignancies express carboxy-anhydraseIX , which has been identified as a novel target for CAR T cell treatment. Normally, the metalloprotease (CAIX) catalyses the hydration of carbon dioxide, however it also functions as a key antigen in renal cell cancer. And it is mildly expressed in the duodenum, small intestine, stomach mucosa, and biliary tree, among other normal tissues[15,16,17].

5. Gastric cancer

Recent research demonstrated that the use of CAR T cells, either alone or in conjunction with the chemotherapy drug Paclitaxel or CAR T cells modified INTERLEUKIN-12 release, is a promising strategy that significantly improves the quality of life for patients with ICAM-1high-advanced gastric cancer[18].

Limitations of car-t cell therapy

1.Antigen escape

Tumor resistance to single antigen targeting CAR constructions is one of the most difficult limitations of CAR-T cell therapy. The malignant cells of a sizable fraction of patients treated with these CAR-T cells show either partial or complete loss of target antigen expression, despite the fact that single antigen targeting CAR cells initially have the potential to produce high response rates. Antigen escape is this phenomenon's scientific name. Many approaches currently rely on targeting numerous antigens to decrease the relapse rate in CAR T cell treatment of both haematological malignancies and solid tumours[19,20,21].

2. On-target off-tumor effects

The fact that solid tumour antigens are frequently and at varied degrees expressed on normal tissues makes it difficult to target solid tumour antigens. Antigen selection is therefore essential in CAR design to prevent "on-target off-tumor" harm and to guarantee therapeutic efficacy. The targeting of tumor-specific post translational changes represents a potential strategy to circumvent the targeting of solid tumour antigens that are also present on normal tissues. There have been studies on four primary CAR-T cell targets, including (TAG7228, B7-H3 ,MUC1 16 and MUC16) In order to increase the clinical usage of CAR-T cell therapies, additional creative ways to stop antigen escape and choose antigens capable of producing a significant antitumor activity while minimising safety issues would be required[22,23].

3.Immunosuppressive microenvironment

Numerous immune-suppressive cell types, such as myeloid-derived suppressor cells, tumor-associated macrophages, and regulatory T cells, can infiltrate solid tumours in the tumour microenvironment. Growth factors, cytokines, and chemokines that promote tumour growth are produced as a result of these infiltrates and tumour cells. Poor T cell multiplication T cell persistence are two of the key reasons for no response or a subpar response to CAR-T cell treatment. It has been proposed that coinhibitory mechanisms are what start the development of this T cell fatigue. Due to the fact that it offers the two components required for potent immune responses, combination immunotherapy using CAR-T cells and checkpoint blockade is considered to be the next step in immunotherapy[24,25,26].

4. CAR-T cell trafficking and tumor infiltration

Solid tumour CAR-T cell therapy is more limited than CAR-T cell therapy for haematological malignancies because CAR-T cells can only travel to and enter solid tumours through physical tumour barriers such the tumour stroma and an immunosuppressive tumour microenvironment. Utilizing delivery methods other than systemic delivery is one way to address these drawbacks since local administration (1) decreases the requirement for CAR-T cells to travel to disease areas and (2) reduces toxicities that occur when CAR-T cells treat tumours but do not directly target normal tissues. The expression of chemokine receptors that are compatible with and responsive

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to tumor-derived chemokines on CAR-T cells is one recently discovered method that looks to dramatically improve CAR-T cell trafficking[27,28].

Advantages of car - t cell therapy

The sudden early impact and single CAR T cell injection are CAR T cell therapy's most prominent advantages over other cancer therapies.Furthermore, the patient only needs good care and surveillance for two to three weeks.CAR T cell therapy is referred to as a "medicine of the present day" and its effectiveness may last for decades due to the cells' longterm survival in the host body and ongoing capacity to identify and eradicate cancer cells upon recurrence.For individuals for whom transplantation has not been curative and who relapse after transplant, CAR T cell treatment is currently approved for usage.

It is anticipated that CAR T cell treatment would replace various transplants.Clinical trials on blood cancer have demonstrated that CAR T cell therapy was effective in totally curing the disease, even in individuals with a refractory condition in which cancer relapsed after multiple transplants (118). Patients can also live a normal life free from the threat of relapse and gain access to curative treatments like stem cell transplants thanks to CAR T cells. As a result, CAR T cell treatment is sometimes called a "living medication."[29-33]

Future prespective

Blood malignancies that express CD19 seem to respond best to CAR-T cell therapy for a number of well-explained reasons. The distinctive characteristics of CD19 as a target include its high levels of tumour antigen expression, ease of physical access to tumour cells via the blood and lymphatics, and the tolerance of the on-target off-tumor effect of B cell aplasia. The technical design of CAR-T cells has undergone a number of advancements, though, in an effort to boost effectiveness and lessen toxicity in haematological malignancies and address the problems associated with solid tumours. Multiple antigen targeting is one strategy gaining attention with the goal of increasing specificity, catching different tumour clones, and lowering antigen-negative relapse.

The best documented example of this secretes IL-12 upon encountering the target antigen, altering the tumour microenvironment in favour of immune activation and tumour cell death. Cytokine release by T cells guided for universal cytokine killing .With the addition of chemokine receptors to facilitate trafficking or components to detect and activate in the presence of hypoxia, further advancements have made it possible to use the hostile tumour microenvironment to guide and activate CAR-T cells[34-36].

II. DISCUSSION

Blood malignancies that express CD19 seem to respond best to CAR-T cell therapy for a number of well-explained reasons. The distinctive characteristics of CD19 as a target include its high levels of tumour antigen expression, ease of physical access to tumour cells via the blood and lymphatics, and the tolerance of the on-target off-tumor effect of B cell aplasia. The technical design of CAR-T cells has undergone a number of advancements, though, in an effort to boost effectiveness and lessen toxicity in haematological malignancies and address the problems associated with solid tumours.

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