

Advances in Chimeric Antigen Receptor T Cell Therapy: A Short Review

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Abstract

Advances in cancer therapy or diagnosis are offered by immunotherapy, there are several approaches of immune therapy to counter cancer. Conventional cancer chemotherapy relied, killing the cancer cells by cytotoxic drugs. Due to toxic effects of the drugs on the patient and also the drug induced cancer with variety of adverse drug reactions. The cancer therapy was much failed. The quality of life of patients and high economic cost of drugs was very much discouraging for the patients. The new therapy in which immune system is applied no such side effects and new drug induced cancers that are not observed. The immune therapy can be described as utilizing own immune system to counter the cancer. The immune therapy has several streams of treatments such as checkpoint inhibitors, adoptive cell transfer, monoclonal antibodies, vaccines for the treatment of cancer. In this article we are discussing chimeric antigen receptor T cell therapy with other immune therapy.

Keywords: CAR-T Therapy; Immunotherapy; Adoptive T-Cells Therapy; TCR Therapy

Introduction

Thymus derived T-cells modified with chimeric antigen receptors T-cells (CAR-T) are successfully used in the immunotherapy of soft cancer cells such as hematologic malignancies. Its effect on solid tumours, is explored as treatment has encountered several obstacles associated with the multiple mechanisms of immune suppressive microenvironment [1,2]. CAR-T therapy is based on using patient's immunologic system to resolve the cancers in the same patient. In a simple way, in the CAR-T therapy the blood of the patient is harvested for white blood cells which are thymus derived. These cells are cultured in-vitro and challenged with antigens from cancer. Now, the T-cells become responsive for the cancer and starts making antibodies for the cancer [3]. These cells are again injected into the patients system which is described as ex-vivo. The new sensitized cells, are capable of identify antigens of the cancer and killing them. This type of treatment offers many advantages over conventional cancer therapy. All the areas of anticancer drugs except sensitization of allergic manifestations are not observed. The treatment is targeted and does not affect other tissues and spares the other parts of the body where it is not required [4].

Chimeric antigen receptor modified T-cells targeting the CD-19 and CD-20 have been found very useful in the treatment of blood cancers. It is interesting to know that studies on CD-19 and CD-20 are showing promising response in relapsed and refractory B-lymphoma

and leukaemia especially in acute lymphoblastic leukaemia cells. The efficacy of chimeric CAR immune therapy in animal models of solid tumors is found to be encouraging and worth exploring further [5,6]. US-FDA has recently approved some CAR-T therapy for variety of diseases as shown in table 1.

S. No	CAR-T therapy	Therapeutic uses	Targeted antigen
1	Tisagenlecleucel (Kymriah)	B-cell precursor acute lymphoblastic leukemia (ALL)	It is a CD19-directed genetically modified autologous T cell immunotherapy.
2	Axicabtagene ciloleucel (Yescarta)	Relapsed or refractory large B-cell lymphoma	It is a CD19-directed genetically modified autologous T cell product
3	JCAR017*	Aggressive B-cell non-Hodgkin's lymphoma (NHL)	CD19 -directed 4-1BB CAR-T cell product

Table 1: Approved CAR-T product by FDA.

*Phase-I development stage.

The challenges in CAR-T therapy

The existing challenges in CAR-T therapy are precise tumour targeting to avoid the off-target toxicities. Adequate T-cell infiltration and migration to the solid tumours for better control of CAR-T cell activation, proliferation and persistence of CAR-T cells side effect management prevention of genome toxicity of insertional mutagenesis and malignant transformation derived from viral vector, transduction and gene editing. Strategization of manufacture and cost control of the logistics issues with the CAR-T therapy. There are significant improvements in novel CAR-T cell therapies [7]. There are several approaches for CAR-T therapy as shown in figure 1.

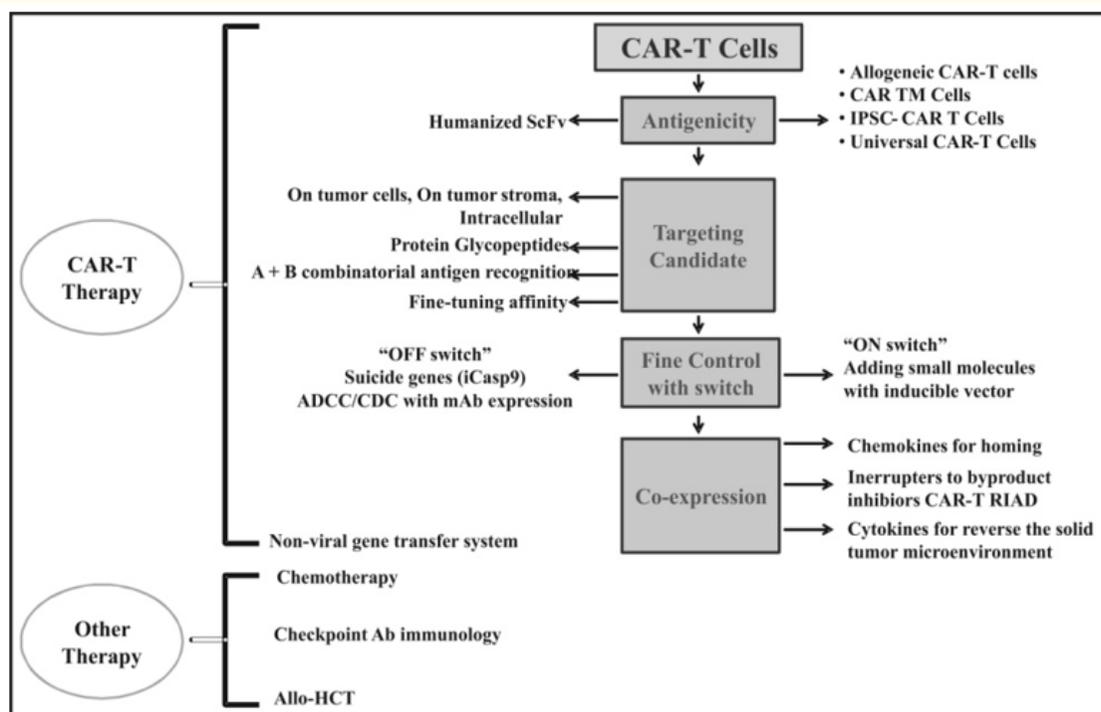


Figure 1: Approaches for CAR-T therapy.

T-cell based therapy uses genetically modified allogeneic immune cells. Allogeneic means it is involving or derived from or being individual of the same species. They are sufficiently unlike genetically to interact antigenically. It is denoting tissues or cell from the same species but genetically distinct. As per the transplantation biology, it means tissues particularly stem cells either from bone marrow or peripheral blood that are from the same species but the antigenically distinct. Allogeneic cells are those obtained from the individual of the same species for the purpose of transplantation from one person to another person [8].

In contrast autogenic means a stem cell transplant procedure during which the doctors either replace the diseased or ineffective stem cells with the healthy new stem cells. Stem cell, transplant the diseased or ineffective stem cells with healthy new stem cells are allowed to a high dose treatment of lymphoma and some testicular cancers. It is often life saving for patients with blood cancer and many serious blood disorders. The patient may be requiring the stem cell transplant for different causes like when the body is unable to make the blood cells like aplastic anaemia or they may have a disease due to high dosage of chemotherapy and radiation therapy.

The major types of stem cell transplants are autologous and allogeneic transplants. Both kinds of stem cells transplantation are common treatment option for non solid cancers like leukaemia, lymphoma and multiple myeloma. The autologous transplant uses a person's own stem cells. The stem cells are deposited in the stem cell banks and frozen in liquid nitrogen before transplant. Where in allogeneic transplant uses stem cells from a donor, whose human leukocyte antigen (HLA) are acceptable and match to the patients HLA. The stem cell donor may be a relative or non-relative and identified through a donor registry. In allogeneic transplant there are two types viz myeloablative transplant where in large dosage of chemotherapy and radiations are used to overcome resistance and eradicate the patient's malignancy. The other type, that is reduced intensity allogeneic transplant, doctors suppress the immune system of the recipient so that the donor cells can become acceptable and in grafted in place of recipient's immune cells. The intensity of the therapy is mild and it is not aimed to eradicate the malignancy. This transplantation aims at immunologic recognition of the cancer by the immune system of the donor, this is described as graft versus tumor effect. Reduced intensity allogeneic transplant are also used to treat many blood disorders and disorders of the immune system such as aplastic anemia, sickle cell anemia, myelodysplastic syndrome, waldenstrom's, macroglobulinemia, myeloproliferative disorders. The process of growing new blood cells after transplants takes 2-4 weeks as the stem cell transplant destroy and rebuild the immune system in patients. During that period they become vulnerable to infections from common bacteria and fungi because they are immune compromised. The full recovery of the immune system can take much longer time.

Recent advances in CAR-T therapy

Transduced T-Cells, adoptive T-cells therapy (ACT) and Gene-engineered T cells

CAR-T therapy efforts were made to engineer T cells expressions of antigens for improving the efficacy. Efforts were made to construct T cell receptor-transduced T cells (TCR-T) to understand how the adoptive T cell therapies (ACT) are developed. Although this adoptive T cell therapy appear to be a very promising. The dark side of this therapy is the tumor associated antigen (TAA), multidimensional interaction of tumour and normal tissue aggravate the uncontrolled results of T-cells gene therapy, which is very much complicated. Hence they are optimizing treatment security to avoid a lethal adverse event. Now the efforts are on to optimize the treatment and balance the safety verses efficacy of the ACT [8]. A multidimensional tool of tumor immunotherapy is tried with gene-engineered T cells (GE-T) along with radiation therapy, tumor vaccination is being developed. A network to connect radiation therapy, tumor vaccines, CAR-T and TCR-T is being built. It is very much expected the combination of ACT and other therapies would further enhance efficacy of the GE-T [5,9].

Different subsets of T cells

The CAR-T cells are capable of recognizing the tumour antigens and inducing cytotoxic activities against tumour cells. It has been discovered that functionally differences in T-cells like memory T-cells and effector T-cells are laying an important role in CAR-T cell immunotherapy. The CD-4⁺ subsets (Th1, Th2, Th9, Th17, Th22, Treg and Tfh) and CD8⁺ memory and effector subsets differ in extracellular (CD-25, CD45RO, CD45RA, CCR-7 and L-Selectine). The intercellular markers (FOXP3), epigenetic and genetic programs; and metabolic

pathways and these properties can be modulated to sharpen CAR-T therapy. CD-4⁺ Treg cells suppress the efficacy of CAR-T cell therapy and different approaches to overcome this suppression. Next revolution in CAR-T immunotherapy is aimed at improving the CAR-T therapy by scoring knowledge of T-cell subsets functions, differentiation, proliferation and signalling pathways to generate more active CAR-T cells tools [11,12].

TCR therapy

Recent breakthroughs in T-cell based immunotherapy is the adoptive transfer autologous tumor infiltrating lymphocytes (TILs) as well as T-cell introduced with genetic material encoding in T-cell receptors (TCR) or chimeric antigen receptors. The design of CAR links antibody mediated recognition of cancer associated antigens with the cytotoxic activities of immune effector cells. TCR and CAR directed T-cells unable to recognize antigen and be activated to be effector cells as shown in figure 2. One should realise that each strategy is unique and as distinctive advantages and disadvantages. TCR directed T cells recognize the antigen in a human leukocyte antigen. This design boosts cellular immunity and overcomes the HLA restriction and tumor evading mechanisms. This is the promising mechanism because of the potential for large number of clinical applications [13,14].

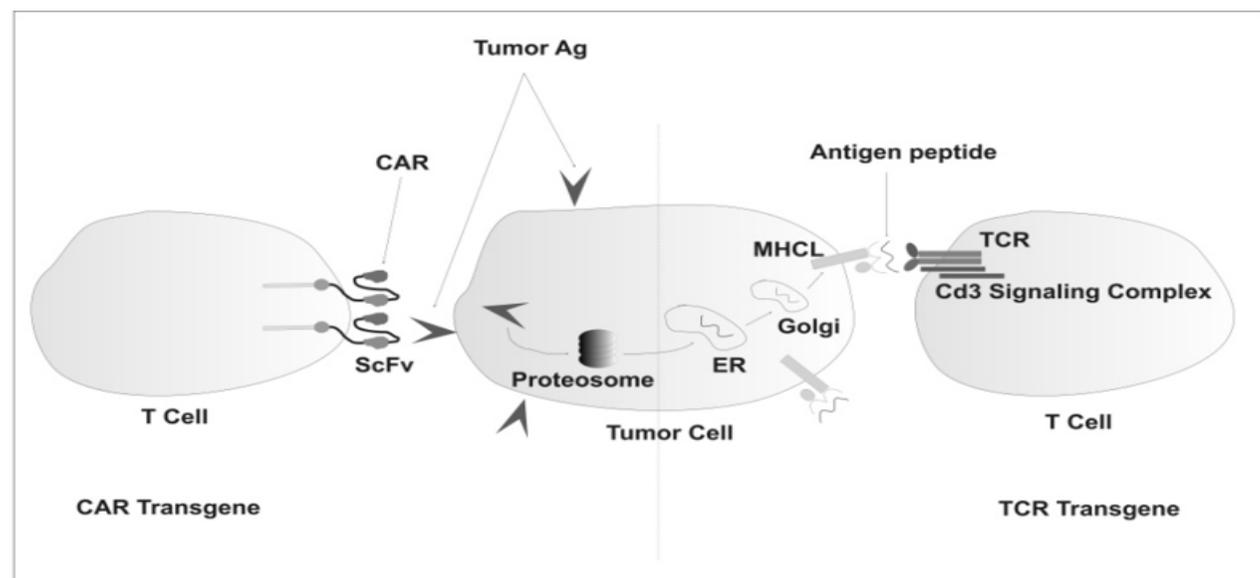


Figure 2: Schematic representation of genetically modified T cells with CARs or TCR, MHCL: major histocompatibility complex I, ER: endoplasmic reticulum, ScFv: extracellular single-chain antibody domain (scFv), Tumor Ag: tumor antigen.

The TCR therapy helps to reconstitute Hepatitis B virus (HBV) immunity in patients who are chronically infected are to target tumors expressing HBV antigens in patients with hepatocellular carcinoma because regular stimulation would have caused functional deletion due to exhaustion. However intermittent stimulation will give opportunity to rejuvenate the TCR mechanism. HBV specific TCRs are cloned from T cells obtained from patients with acute resolved HBV infection and TCR associated. The TCR of known specificities are transfer to T cells from patients using retroviral transduction mRNA by electroporation. TCR gene modified T cells targeting has been validated in-vitro and in-vivo has been validated in xenograft mouse model. Translation of application of TCR gene modified T cells from the bench to bedside for treatment of HBV related patients is been worked on. The objective of using T cells is non cytopathic antiviral activity

for adoptive cell therapy in chronic HBV patients. Recent methods of generating tumor specific T cells include the genetic modification of patients lymphocytes with receptors to provide them with tumor specificity. These T cells are then expanded in-vitro followed by infusion of the patients in adoptive cell transfer protocols (ex-vivo). Genes used to modified T cells include those encoding T cell receptors and chimeric antigen receptors [15].

The design of CAR links antibody mediated recognition of tumor associated antigen with the cytotoxic activities of immune effectors cell directly. CAR-T cells can be activated directly via CARs independent of human lymphocyte antigen (HLA). The CD8⁺ CAR-T cells are activated and delivered to granzyme B and perforin mediated cytotoxicity as normal cytotoxic T cells. CD4⁺ CAR-T cells and also be activated through CARs in an HLA independent manner to become helper T (Thymus cells). Helper T thymus cells secrete cytokines to regulate the immune response. The activated CAR CD4⁺ T cells provide support to CAR CD8⁺ T cells, CD4⁺ T and CD8⁺ T cells which are usually different but genetically modified with CAR. These cells are then infused into the patients (ex-vivo) and boost the cellular immunity and over come the HLA restrictions and some tumor escape mechanisms. CART cell therapy is highly complex there are so many doubts such as safety targeted tumors about T cell and tumor interaction is also not clear how to make T cell Fight with tumor microenvironment efficiently and optimize the T cell gene transfers. The standardization of the protocol of production and controlled the cost of cell manufacture for clinical practice. The main barriers to overcome in order to make these therapies available are eliciting and effective immune response in a consistent manner and to address side effects of this immunotherapy [16].

Cluster of differentiation in CAR-T therapy

The immune responsive cancer is dependent on T cells, which are specific for cancer associated antigens. The T cells are capable of recognizing the new epitops generated by mutation or transcriptional aberrations in cancer. Mutant peptides, that bind to MHC class-1 (major histocompatibility complex) and MHC class-2 can generate a protective immunity. Although the role of T cells that expresses the CD-4 in the anticancer immune response is not clear. CD-4 carrying T cells are important in helping to dry both the antibody response and that cytotoxic CD-8 expressing T cells and they can produce interferon gamma, thereby contributing to an inflammatory response that favours antitumor immunity. T cells that carry CD-4 are also known to mediate cytotoxicity in the some tumors such as melanoma can express MHC class-2 molecule often on exposure of interferon gamma and may be the director gets the cytotoxicity CD-4 expressing populations [17,18].

Sub-optimal antigen recognition as a strategy for cancer treatment

The sub-optimal antigen immunotherapy is also known as dendritic cell based cancer immunotherapy. The use of dendritic cells for cancer immunotherapy was first proposed by Steinman and Cohn. Dendritic cells (DC) comprise a heterogeneous group of cell types derived from hematopoietic precursors. They are broadly classified as myeloid DC and plasmacytoid disease. It was discovered that DC cells can also differentiate ex-vivo, when they combined with Granulocyte-macrophage colony-stimulating factor (GM-CSF) and Interlukine-4. The cultured DC cells are immature and this ensures that they can be modified and matured required using the stimuli of immunotherapy. DC present on the surface, a void collection of receptors which recognize a variety of pathogen associated molecular patters are inflammation related cellular protein. The binding of these molecules with their appropriate receptors triggers there phenotypic and function maturation by the strong up-regulation of MHC and co stimulated molecules of antigen presentation [19].

Adverse drug reactions (ADRs) of CAR-T therapy

Immune checkpoint blockage increases the antitumor immunity by blocking the intrinsic down regulation of immunity such as cytotoxic T-lymphocyte antigens, PD-1, PDL-1 by increasing the activity of the immune system. Immune checkpoint blockage can have inflammatory side effects which are often termed as immune related ADRs. Although any organ of the system can be affected, most commonly gastro-intestinal tract, endocrine glands, skin and liver are observed. The central nervous system and cardiovascular pulmonary musculoskeletal and haematological systems are also involved to lesser extent. The immune related adverse events, the participation of

auto antibodies rather than auto reactivity cells is observed. The involvement of cytokines is also so expected in the pathophysiology of immune related adverse events. The management of adverse events is carried out by immune -suppression like glucocorticoids to reduce the excessive state of temporary inflammation.

However the side effects of glucocorticoids like hyperglycaemia, oedema and anxiety. Immunosuppression is an also risk factor for opportunistic infections [20].

Conclusion

Chimeric antigen receptor T cell therapy is a novel, non toxic, targeted anti cancer therapy. Here exploitation of patients own immune system is utilized to eradicate a cancer. The research has diversified into variety of CAR-T therapy which is still under development. One can see some light and the end of tunnel as cancer becomes curable.

Conflict of Interest

The author declares there is no conflict of interest.

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