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CAR T-Cell Therapy: The Next Frontier for Cancer Immunotherapy

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Abstract: Cancer is among the leading cause of death around the world. Till now many different types of therapies, medications have been developed for these neoplastic diseases. But due to their restricted effectiveness in accordance with the heterogeneity of cancer cells, there is a constant need for novel therapeutic approaches with improved success, like an immunotherapy that uses and enhances the capacity of the patient's immune system. Chimeric antigen receptor T cells are T cells that are genetically modified to produce an artificial T cell receptor to target a specific protein. The chimeric antigen receptors are called so as they have both antigen binding and T cell activating functions on a single receptor. CAR T cell therapy uses T cells engineered with CARs for cancer treatment. In this review, we will discuss the basic design of CARs, the different FDA approved CAR T cell therapies in preventing different types of cancer, the factors affecting the therapy and the risks involved around the therapy.

Index Terms **- Chimeric antigen receptors, CAR T cell therapy, Cancer Immunotherapy, tumor, FDA approved therapy.**

I. INTRODUCTION

Chimeric antigen receptor T-cell therapy (CAR T-Cell therapy) is a new adoptive immunotherapy that represents advancements in cancer therapy. T-lymphocytes are genetically engineered using a viral vector carrying a chimeric antigen receptor (CAR). The CAR encodes for an extracellular domain for tumor antigen recognition (such as CD19 to recognize B cells) which is linked to an intracellular signaling domain that mediates T-cell activation. These modified T-lymphocytes are then infused into the patient to target and eliminate cancer cells by utilizing the patient's immune system.

Immunotherapy is additionally termed as biotherapy because the immune system in the body is naturally capable of detecting pathogens and cancerous cells. In recent years, immunotherapy has emerged as an important branch of treatment for similar types of disease; however, its protective mechanism may differ [1, 2]. Certain immunotherapies boost the immune system of the body and on the other hand others immunotherapies directly target the cancer cells in the body. Each treatment type has its advantages and disadvantages depending on the disease type [1, 3].

II. CAR T-CELL STRUCTURE

Ectodomain

The ectodomain is a membrane protein domain located outside the cytoplasm and accessible from the extracellular space. The ectodomain consists of a signal peptide, an antigen recognition region and a spacer region. The function of the signal peptide is to guide proteins to the endoplasmic reticulum. ScFv acts as an ectodomain signal peptide in CAR and consists of the variable parts of heavy and light immunoglobulin chains, which are fused through a flexible linker. Antigen recognition domains are usually ScFvs with simple ectodomains and more foreign recognition components and they can recognize any antigen as long as it can bind to a high-affinity target. The connection between the antigen binding domain and the transmembrane domain is based on a spacer. The spacer is the IgG1 hinge region, which is sufficient for most ScFv-based constructs [4].

Transmembrane domain

The transmembrane domain is the component closest to the ectodomain membrane and is composed of hydrophobic alpha helices across the membrane. The stability of the receptor is associated with the transmembrane domain. The native CD3 - zeta transmembrane can incorporate the artificial TCR into the native TCR. Nowadays, the CD28 transmembrane domain is the most stable receptor [4].

Endodomain

The endodomain is practically stop of the receptor and the component CD3 ζ is blanketed in three layered immunoreceptor tyrosine-based activation motifs (ITAMs). After antigen recognition, the receptors cluster and signalling is activated, then the signal is transmitted to the T-cell. Costimulatory signalling is required during this process [4].

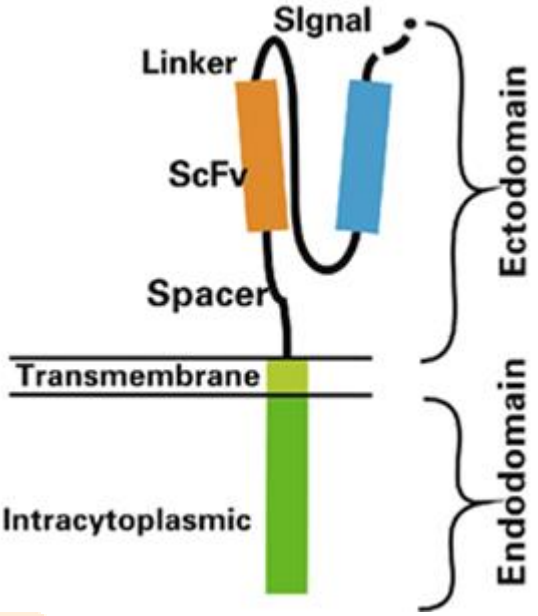

Figure 1 Structure of CAR T Cells [4]

III. Evolution of CAR T-cell

The single chain antibody (CD3ζ or FcεRIγ) binds to ITAM at the transmembrane site during the first generation. The costimulatory or stimulator molecule (CM1), including CD28, has been genetically modified at the signal transduction site for the second generation. Later on, another costimulatory molecule (CM2) is mainly based on the second generation, as the development of the third generation is based on the location of signal transmission, including the combination of CD134 or CD137. Interleukin-12 (IL-12) is mainly based on this on the second generation for the development of the fourth generation and is designed for the place of signal transduction [4,5,6].

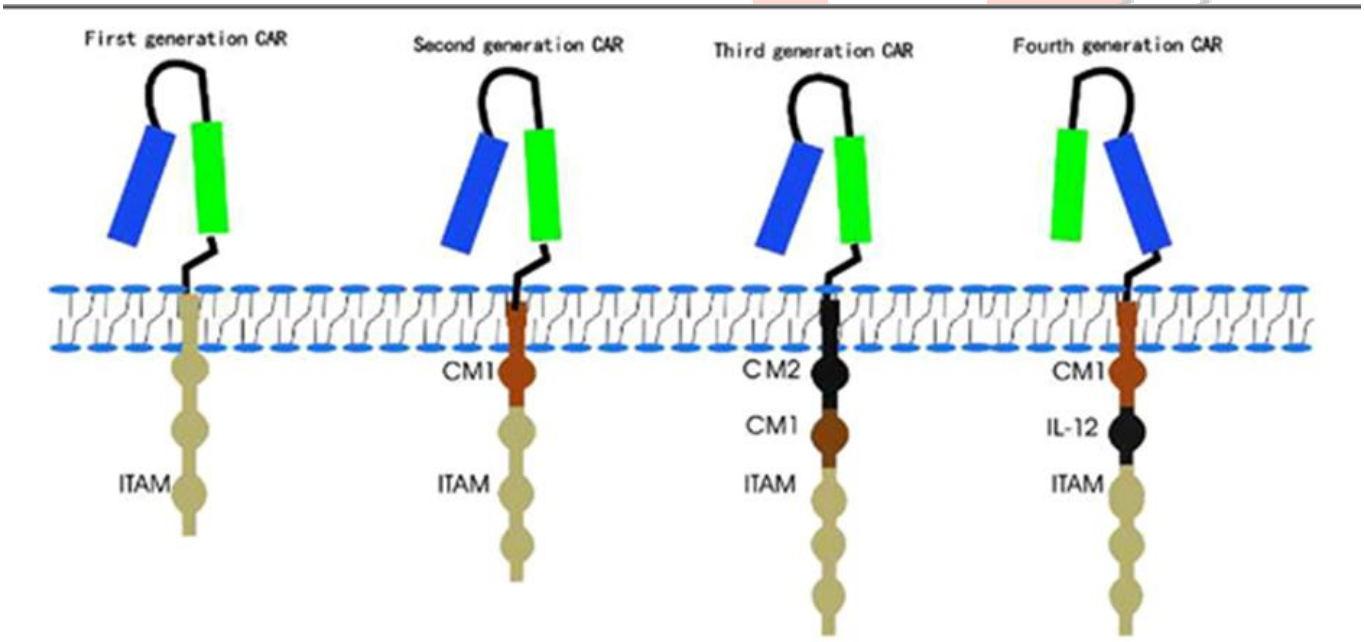

Figure 2 Evolution of CAR T-cell [4]

IV. Mechanism

Effective adoptive T cell therapy (ACT) is made up by the killing of cancer cells via the therapeutic use of transferred T cells. Chimeric antigen receptor (CAR) T cell therapy is one of the main ACT approaches. CAR T cells intervene in MHC-unrestricted tumor cell killing by enabling T cells to bind target cell surface antigens through a single-chain variable part (scFv) recognition domain. Upon binding, CAR T cells shape a non-classical immune synapse (IS). This is required for their effector function. These cells at that point mediate their anti-tumoral effects through the perforin and granzyme axis, the Fas and Fas ligand axis, as well as the discharge of cytokines to sensitize the tumor stroma. Their perseverance within the host and functional outputs are firmly dependent on the receptor's individual components—ScFv, spacer domain, and costimulatory domains—and these components function to meet the expansion of CAR T-cell execution [7].

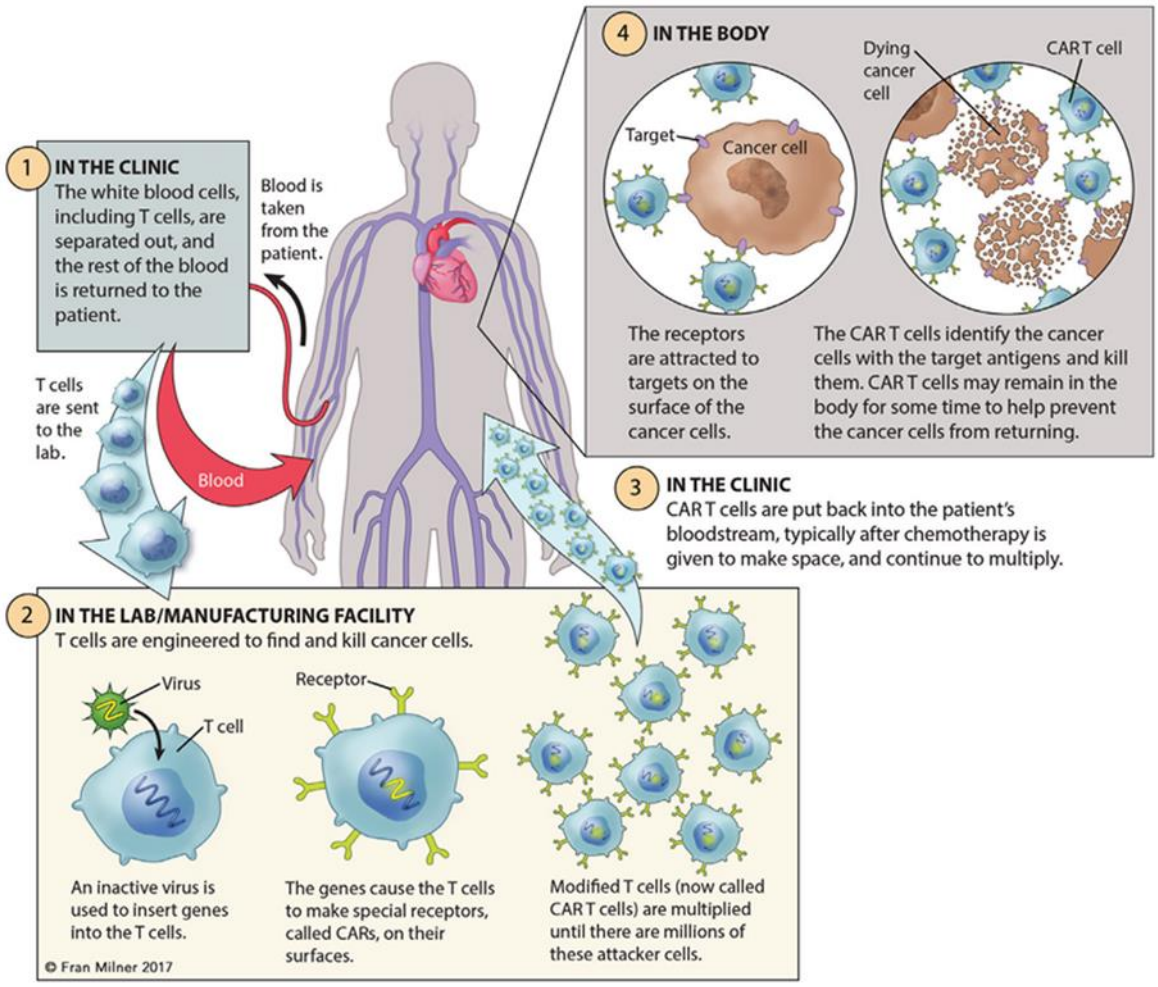

Figure 3 Autologous CAR T-Cell Therapy Process. Source- Leukemia and Lymphoma Society. (2020). https://www.lls.org/treatment/types-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy

V. FDA Approved Treatments

5.1 Axicabtagene ciloleucel (Yescarta™)

Yescarta™ (axicabtagene ciloleucel) is one among first chimeric antigen receptor T-cell (CAR T-cell) therapies. It is used for the treatment of relapsed / refractory large B-cell lymphoma in adult patients. The drug is administered to patients who were earlier treated with two or more lines of systemic therapy. It is not meant for patients with primary central nervous system (CNS) lymphoma [8, 9].

Kite Pharma manufactured and distributed Yescarta. Kite Pharma is a subsidiary of US-based biopharmaceutical company Gilead Sciences. Kite Pharma put forth a biologics license application (BLA) for Yescarta in March 2017. US Food and Drug Administration (FDA) sanctioned it as the second CAR-T therapy, in October 2017. The drug also received breakthrough therapy from the FDA [11].

The company initiated its CAR T-cell clinical program in the EU in August 2017. The drug was approved in August 2018 by The European Medicines Agency (EMA) for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) in adult patients. In February 2019, Health Canada approved Yescarta [8, 9].

Kite Pharma and Fosun Pharma formed a joint venture (JV) named FosunKite in April 2017 for the development, manufacturing and commercialization of the drug in China. The JV also holds the option for additional products including Kite's two T-cell receptor product candidates [11, 12].

5.1.1 Clinical trials on Yescarta

The safety and efficacy results of Yescarta were the basis for the FDA approval. The approval was based on ZUMA-1 study, a single-arm, open-label, phase 2 clinical trial of adults with relapsed or refractory aggressive B-cell NHL [8, 10, 11]. After receiving lympho-depleting chemotherapy, 101 patients (median age, 58 years) received axicabtagene ciloleucel as a single intravenous infusion at a target dose of 2×10^6 CAR-positive viable T-cells/kg (maximum permitted dose of 2×10^8 cells). All patients were hospitalized for the infusion and remained hospitalized for at least 7 days thereafter [12].

In ZUMA-1, 72% of the patients demonstrated an objective response to treatment with axicabtagene ciloleucel, and 51% of patients achieved a complete remission (**Table 5.1**). The median time for treatment response was about 0.9 months (range, 0.8-6.2 months). At a median follow-up of 7.9 months, the median duration of response for patients in complete remission had not been reached (**Table 5.2**) [12].

Table 5.1. Response Rates with Axicabtagene ciloleucel in Patients with Relapsed or Refractory Aggressive B-Cell Non-Hodgkin Lymphoma. Based on 2007 revised Internationa; Working Group criteria, as assessed by the independent review committee. CI indicates confidence interval. Source: Yescarta (Axicabtagene ciloleucel) suspension for intravenous infusion prescribing information; October 2017

Response Rate	Patients receiving Axicabtagene ciloleucel (N=101)
Objective response rate, N (%)	73(72) (95% CI, 62-81)
Complete remission rate, N (%)	52 (51) (95% CI, 41-62)
Partial remission rate, N (%)	21 (21) (95% CI,13-30)

Table 5.2. Axicabtagene ciloleucel's duration of response in Patients with Relapsed or Refractory Aggressive B-Cell Non-Hodgkin Lymphoma. [a]For all responders, the duration of response is measured from the date of the first objective response to the date of progression or death relapse or toxicity. [b]Kaplan-Meler estimate. [c]+ Indicates a censored value. CI indicates confidence interval; NE, not estimable Source: Yescarta (Axicabtagene ciloleucel) suspension for Intravenous Infusion prescribing information; October 2017

Response to treatment	Patients receiving Axicabtagene ciloleucel (N=101)
Responders, N	73
Response duration, mo[a]	
Median[b]	9.2 (95% CI, 5.4-NE)
Range	0.03+ to 14.4+[c]
Response duration, if best response is complete remission, mo	
Median[b]	NE (95% CI, 8.1- NE)
Range	0.4 to 14.4+[c]
Response duration, if best response is partial remission, mo	
Median[b]	2.1 (95% CI, 1.3-5.3)
Range	0.03+ to 8.4+[c]
Median follow-up for response duration, mo[a,b]	7.9

5.2 Brexucabtagene autoleucel (Tecartus®)

The Food and Drug Administration allowed accelerated approval to brexucabtagene autoleucel (TECARTUS, Kite, a Gilead Company), a CD19-directed genetically modified autologous T-cell immunotherapy. This treatment is used for adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Approval was based on ZUMA-2 (NCT02601313), an open-label, multicenter, single-arm trial of 74 patients with relapsed or refractory MCL who had already received anthracycline or bendamustine containing chemotherapy, an anti-CD20 antibody and a Bruton tyrosine kinase inhibitor. Patients receive a single infusion of brexucabtagene autoleucel after the completion of lymphodepleting chemotherapy. The primary efficacy result was objective response rate (ORR) per Lugano [2014] criteria as surveyed by an independent review committee.

From the 60 patients to be evaluable for efficacy of Tecartus based on a minimum duration of follow-up for response of six months, the ORR was equal to 87% (95% CI: 75, 94), with a complete remission (CR) rate equal to 62% (95% CI: 48, 74). The estimated median duration of response was not reached (range of 0+ to 29.2+ months) after a median follow-up time for duration of response of 8.6 months. Of all 74 leukapheresed patients, the ORR as determined by independent review committee (IRC) was 80% (95% CI: 69, 88) with a CR rate equal to 55% (95% CI: 43, 67) [13, 15].

Table 5.3 Comparison of the FDA approved therapies.

Yescarta	Tecartus	Kymriah	Breyanzi	Abecma
October 2017	July 2020	August 2017	February 2021	March 2021
A CD19-targeting CAR T cell immunotherapy	A CD19-targeting CAR T cell immunotherapy	CD19-targeting CAR T cell immunotherapy for adult patients with B-cell precursor acute lymphoblastic leukaemia (ALL)	A CD19-targeting CAR T Cell immunotherapy	A BCMA-targeting CAR T cell immunotherapy
For subsets of patients with relapsed/ refractory large B-cell lymphoma in adult patients	For patients with relapsed or refractory mantle cell lymphoma	To treat adult patients with r/r large B-cell lymphoma	Approved for the treatment of adult patients with relapsed or refractory large B-cell lymphomas	Approved for patients with relapsed or refractory multiple myeloma
$ 373,000	$ 373,000	$ 475,000	$ 410,300	$ 419,500

5.3 Tisagenlecleucel (Kymriah™)

Kymriah™ re-programmes the patient's T-cells with a transgene encoding a chimeric antigen receptor (CAR) and identifying and removing CD19-expressing malicious cells.

Kymriah™ (tisagenlecleucel) is one of the chimeric antigen receptor T-cell (CAR T cell) therapy. In the United States, this treatment is approved for paediatric and young adult patients with B-cell precursor acute lymphoblastic leukaemia (ALL). Penn first developed this drug using a 4-1BB costimulatory domain. The 4-1BB costimulatory domain was used for enhancing cellular responses. Later Novartis joined as a co-developer for the development of the drug. The Oncologic Drugs Advisory Committee (ODAC) of FDA with one accord decided that Ky Mariah's approval in July 2017 is needed. Later it received full approval from FDA in August 2017.

The FDA also approved the drug to treat patients with the following disorders in May 2018

- relapsed or refractory (r/r) large B-cell lymphoma
- diffuse large B-cell lymphoma (DLBCL)
- high-grade B-cell lymphoma and DLBCL resulting due to follicular lymphoma after two or more lines of systemic therapy

In August 2018, Kymriah™ was approved by the EC. It is used for the treatment of B-cell ALL in paediatric and young adult patients, as well as for adults with r/r DLBCL.

5.3.1 Clinical trials on Kymriah

Kymriah™ was approved by FDA on the basis of the results derived from a pivotal open-label, multi-centre, single-arm Phase II clinical trial. This trial was named as ELIANA. The trial in the US, EU, Canada, Australia and Japan. Around 25 centers were a part of this trial. It saw a total of 88 patients infused with Kymriah™. The study demonstrated that 83% of the patients treated with Kymriah™ achieved complete remission (CR) with incomplete blood count recovery (CRi) within three months of infusion. Results which were studied after 63 patients were treated with Kymriah™. It was observed that six months were relapse-free survival and no minimal residual disease (MRD) was observed, which is an indicator for potential relapse detected among patients [14].

5.4 Lisocabtagene maraleucel (Breyanzi®)

The U.S. Food and Drug Administration approved Breyanzi (lisocabtagene maraleucel), a cell-based gene therapy to treat adult patients with certain sorts of large B-cell lymphoma who have not reacted to, or who have relapsed after, at a minimum of two other types of systemic treatment. Breyanzi, a chimeric antigen receptor (CAR) T-cell treatment, is the third gene therapy approved for certain types of non-Hodgkin lymphoma, including diffuse large B-cell lymphoma (DLBCL). Breyanzi is not shown for the treatment of patients with essential central anxious framework lymphoma.

The safety and efficacy of Breyanzi were set up in a multicenter clinical trial of more than 250 adults with refractory or relapsed large B-cell lymphoma. The total remission rate after treatment with Breyanzi was 54%.

Breyanzi when used has severe side effects. The labeling carries a boxed caution for cytokine release syndrome (CRS), which may be a systemic reaction to the activation and multiplication of CAR T-cells, causing high fever and flu-like symptoms and neurologic toxicities. CRS and neurological events can be life-threatening. Other side effects incorporate hypersensitivity reactions, serious infections, low blood cell counts, and a weakened immune system. Side effects generally show up inside the first one to two weeks taking after treatment, but a few side effects may occur afterward.

The FDA granted approval of Breyanzi to Juno Therapeutics Inc., a Bristol-Myers Squibb Company [37].

5.5 Idecabtagene vicleucel (Abecma™)

Abecma was approved by FDA for the treatment of adult patients with relapsed or refractory multiple myeloma. This approval was after four or more prior lines of treatment, such as an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Idecabtagene vicleucel is the first FDA-approved cell-based gene therapy for multiple myeloma.

Idecabtagene vicleucel is a B-cell maturation antigen (BCMA). It is genetically modified autologous chimeric antigen receptor (CAR) T-cell therapy.

Safety and efficacy were evaluated in a multicenter study of 127 patients with relapsed and refractory multiple myeloma who received a minimum of three prior lines of antimyeloma therapies; 88% had received four or more earlier lines of treatments. Efficacy was assessed in 100 patients who received idecabtagene vicleucel within the dosage range of 300 to 460 x 106 CAR-positive T cells. Efficacy was established based on overall response rate (ORR), complete reaction (CR) rate, and duration of response (DOR), as assessed by an Independent Response committee using the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma.

The ORR was found to be 72% (95% CI: 62%, 81%) and CR rate was about 28% (95% CI 19%, 38%). Approximately 65% of patients who achieved CR remained in CR for a minimum of 12 months [38].

VI. BENEFITS

The best-known case of a patient who benefited from CAR T-cell therapy is Emily Whitehead, a girl with relapsed acute lymphoblastic leukemia (ALL) who has now survived cancer for 5 years. Chemotherapy can be used to reduce the tumor burden prior to CAR T-cell therapy. Hematopoietic stem cell transplant (HSCT) to provide additional healing potential. This suggests that CAR T-cells could offer significant clinical benefit regardless of HSCT consolidation. In addition, it is often overlooked that a significant proportion of patients in the same studies go into remission after a previous CAR T-cell transplant, suggesting that graft-insensitive leukemia diseases may be T-cell sensitive. Exceptions are more than 50% CR is observed in a phase. Clinical study for neuroblastoma patients, as from the above examples, CAR T-cell assays differ in many parameters including disease entity, disease burden, disease design, production and amplification of CAR T-cells, patient preconditioning and doses administered. Given this complexity, the identification of the most important parameters for a positive clinical outcome is the focus of the studies on T-cells with CD19-CARs, which showed a significant benefit for the patient. CARs generally belonged to the second generation. However, many other CAR CD19 T-cell studies that also used second generation CARs showed less promising results. Unknown parameters influencing the positive outcome Lymphodepletion has been shown to be beneficial for the expansion and persistence of CAR T-cells in vivo, while concomitant administration of IL- 2 is not recommended. Another important factor influencing expansion in vivo is the phenotype of CAR T-cells. Products containing higher amounts of CAR T-cells with a central phenotype (CD62L +) and/or stem cell memory (CD45RA +) showed improved expansion in vivo. In particular, this phenotype can be maintained during production by using IL. -7 and IL-15 instead of IL-2 for culture. Such CAR-T cells may be less depleted after repeated antigen-specific stimulation. A few other advantages of the CAR T cell therapy is the short treatment duration - around two weeks are required for the treatment to complete. The recovery and remission rates are higher than other cancer treatments. [16,17,18].

VII. FACTORS AFFECTING THE THERAPY

Factors affecting the efficacy of CAR therapy, including CAR structure, in vitro culture system, gene transfer strategies, target selection, and preconditioning regimens.

T cells are usually divided into subsets, each expressing varying persistence and functionality. Theoretically, all cell subsets are often used for CAR cell engineering. However, given the clinical feasibility, the foremost common formulation utilized in current clinical trials are CD4+ T-helper cells plus cytotoxic CD8+ T cells. CD4/CD8 CAR cell efficacy, cytokine production, antitumor activity, and proliferation depend upon subpopulations and ratios used [19]. Both CD4 and CD8 work together to eliminate tumors is indicated by preclinical studies. CD8 T cells are the most effective cytotoxic cells in terms of tumor elimination, whereas CD4 T cells produce the cytokines that are critical for CD8 T cell function. CD4 T cells also kill tumor cells directly.

Just as the foremost effective scFv varies with tumor type, optimal spacer design also depends on the precise tumor epitope being targeted [20, 21]. Spacers are devised carefully. They offer flexibility and enhanced antigen binding, but when they are used incorrectly can inhibit CAR cell efficacy in vivo [20, 21].

Gene transfer technologies allow scientists to engineer lymphocytes with the required CAR structure. While a variety of those methods, both viral and non-viral, are capable of introducing CAR constructs in T-cells, each technique has advantages and disadvantages relying on the investigative purpose.

CAR T-cell in vitro culturing are often divided into five steps: T-cell collection and purification, activation, transduction, expansion, and reinfusion (Figure 1). Suitable T cells collected from blood or tissue samples aren't naturally present in large enough numbers for successful CAR therapy. In vitro expansion of those cells is important, yet prolonged expansion can generate harmful effects on the cells' in vivo persistence [22].

Many factors lead to the success of CAR cells. Persistence and proliferation are futile and dangerous until the proper target antigen is chosen. On-tumor/off-target toxicities caused by unsuitable targets are a major concern in CAR T cell therapy. The expression of Low levels of the target antigen on off-target organs triggers adverse effects.

Despite the success of recent clinical trials, CAR T cell therapy needs to be managed properly or else can induce severe toxicity. Like when the targeted tumor antigen also surfaces on healthy tissue. This threat leads to a furtive look for tumor-specific antigens during preclinical studies.[23]

VIII. Risk Factors

Factors that correlate with increased risk of Immune effector cell-Associated Neurotoxicity Syndrome (ICANS) include high tumor burden, lymphodepletion with cyclophosphamide and fludarabine, high CAR T-cell dose, and high ferritin and cytokine levels [24]. Several studies have also shown that severe (often defined as grade 3 or 4) CRS is a predictive marker for the development of severe ICANS [25].

Another observed side effect of the therapy is the cytokine release syndrome (CRS). CRS is observed when the immune system responds to an infection. As CAR T cells multiply, they can release large amounts of chemicals called cytokines into the blood, which can ramp up the immune system.[26] In this case, symptoms such as fever, chills, nausea, headache are seen. This results in the transformation in the growth factor-β (TGF-β) and interleukin (IL) 10 and hinders the efficiency of CAR T cells [16, 27].

Other possible serious side effects of CAR T-cell therapy can include:

- Allergic reactions during the infusion
- Abnormal levels of minerals in the blood, e.g. low potassium, sodium, or phosphorous levels
- A weakened immune system, resulting in increased risk of serious infections
- Low blood cell counts, which can increase the risk of infections, fatigue, and bruising or bleeding [26]

IX. Challenges Delivering This Therapy

The different challenges associated with CAR T cell therapy are physical barriers, antigen heterogeneity, lack of infrastructure, cytokine release syndrome (CRS), ability of CAR T cell to bind to CD-19 epitome on tumor cells, patients with cancer at higher stages and manufacturing challenges. The challenges delivering CAR T cell therapy must be overcome with more research in this field as in the phase trials, 82% of the patients responded positively to this therapy [28, 29].

CAR-T cell therapy needs to be delivered with utmost care and an established multidisciplinary team. The team should be able to deal with complications in the therapy. The experts who need to be a part of the team are haematologists, intensivists, neurologists, cardiologists and renal physicians. The patients should be well informed about the complications which can occur and the care which they should take after the successful delivery of the therapy for speedy recovery [30]. There are also a few infrastructural hurdles that need to be surpassed by establishing more clinical centers. There is a lack of knowledge or guidance for this therapy currently, at many places CAR T cell therapy is not in practice as CAR T cells are genetically modified organisms (GMOs). Specific guidelines should be made which will specify the characteristics and applicability of the CAR T cells [16].

Antigen heterogeneity is one of the major barriers which hinder the T cells to detect the cancer cells, because of this the effectiveness of CAR T cell therapy reduces. As CARs are easily able to target tumor associated antigens (TAA), the various expressions of TAA by diverse types of tumor cells is another barrier. To add to this, as the antigen expression is different at different tumor sites, it may inhibit the working of CAR T cells at the tumor site because the cancerous cell antigen range makes it pretty much tough to locate the tumor-specific antigens [31, 32].

CAR T cells are always in contact with the bloodstream and lymphatic system but these cells cannot pass through the vascular endothelium so this therapy has a limited scope in solid tumors than in hematological tumors [6,31].

Sometimes it is difficult for CAR T cells to spread across the tumor bed as some tumors release chemokines, CXCL12 and CXCL5, which do not allow T cells to spread into the intra-tumoral site. Another challenge that needs to be looked at is the physical barrier, the extracellular matrix has many effects on tumors and the immune system. One of the proteins in the extracellular matrix, heparan sulfate proteoglycans (HSPGs), is a non-structural matrix and helps in tumor cell proliferation and migration. Therefore, it becomes difficult for the CAR T cells to penetrate in tumor sites and disrupt them. So, the T cells need to be specifically modified to penetrate and kill the tumor cells without reducing the cytotoxicity [27].

Currently, the CAR T cell products are manufactured using autologous T cells, the T cells are derived from the patients who are undergoing the treatment. This is a very personalized and limited form of treatment. Sometimes the patients with cancer do not have sufficient numbers of naïve T cells due to several reasons, one of which being previous chemotherapy. As the manufacturing process is lengthy, is it not advantageous for patients with advanced stage cancer. If there is a hurry in the manufacturing process, then it might result in poor response rates in patients. CAR T cells produced from allogeneic donor T cells than from autologous donor T cells can evade the manufacturing issues of inadequate cell numbers, suboptimal T cell states and delay in treatment [18,28].

X. Value And Affordability

Tisagenlecleucel and Axicabtagene Ciloleucel (Axicel) are the first two commercially produced CAR-T cell therapies. These therapies have shown long-term disease control. Given the high price of a single infusion of CAR T cell therapies ($ 373,000 for Axicel and $ 475,000 for Tisagenlecleucel), the high list price for Tisagenlecleucel does not reflect the total cost to payers of each cycle of CAR T-cell therapy, the number does not include the costs associated with pheresis and cell infusion. Management of complications, including frequent hospital and intensive care stays and the use of the anti-IL-6 receptor antibody tocilizumab, which was approved concurrently with tisagenlecleucel for the treatment of SRC1. In a study, 53 of 68 patients (78%) developed CRS after receiving Tisagenlecleucel, and 32 of these 53 patients (60%) had Grade 3 or 4 CRS; hence, the use of supportive services will be substantial. In addition, up to half of all patients who respond to CAR T-cell therapy will relapse at some point and therefore many providers will seek to consolidate initial therapy. Allogeneic stem cell transplant is one of the treatments to ensure permanent remission. It is estimated that the allogeneic transplant costs $ 200,000. In short, $ 475,000 is just the tip of the iceberg when you factor in the total cost of treatment with Tisagenlecleucel. The Centers for Medicare and Medical Services (CMS) are negotiating with Novartisto to enter into a performance-based pricing contract under which CMS pays Tisagenlecleucel only if a patient has a response within one month of the treatment. Given that 50 of the 63 evaluable responders (79%) in a study responded to this drug within a month, 13 is a 1-month results-based discount could essentially translate into a price of $ 377,000 per dose (79% of $ 475,000). However, such a policy does not include reimbursement of ancillary services or the cost of patients who initially respond to therapy but later relapse. In particular, 46% of those who resort to therapy, the response to tisagenlecleucel in a trial had a disease relapse within 12 months. If Novartis also reimbursed patients whose disease recurred at that time, the payers would essentially be paying approximately $ 200,000 per patient infused [33, 34].

Manufacturing CAR-T cells toward commercialization

Autologous cell-based therapies present a different set of manufacturing challenges. In contrast to the concept of scaling up allogeneic donor manufacturing in large quantities, scaling up for patient-specific manufacturing of CAR-T cells requires the ability to accommodate multiple independent productions in parallel. Nowadays, CAR T cell producing platforms are labor intensive. Problems related to quality control and the release of individual batches add to the complexity of the individual manufacture and increase drastically the cost of the goods. Pharmaceutical and biotech companies are entering the field of adoptive cell therapy. The most extensive experience in CAR-T manufacturing is still in academic centers today; partnerships between industry and academic centers such as JUNO Therapeutics and the Memorial Sloan Kettering Cancer Center, Novartis and the University of Pennsylvania, Kite Pharmaceuticals and the National Cancer Institute facilitate the process. We need to transfer, improve, accelerate, development and promote future commercialization prospects for this promising therapeutic modality. The challenges of developing a controlled and profitable manufacturing process have not yet been overcome. Therapeutically active T cells or subsets of T cells have yet to be identified in the manufacturing of raw material. The complicated manufacturing process needs to be simplified in order to promote standardization and produce products with an improved defined composition. Implementing fully closed systems to mitigate costly environmental requirements for cGMP manufacturing, such as: GMP systems and labor-intensive environmental monitoring plans, as well as automation to prevent errors introduced by the operator, are also pressing issues. Indeed, it is necessary to develop and test new manufacturing tools [35, 36].

XI. CONCLUSION

CAR T-cell technology is the first clinically approved gene therapy and gene editing tool in CAR T-cell product studies. The development of CAR T-cell therapy is a promising therapeutic option for patients with advanced malignancies, particularly blood disorders. However, the success has been limited due to B cell abnormalities. These approaches will benefit our ability to create genetically engineered T-cells, to support desired new activities and help them target solid tumor cells and survive and function in hostile circumstances. The cost of manufacturing CAR T-cells and particularly time involved in producing clinical-grade retroviruses, is one of the many factors that play a role in the production of CAR T-cells. However, there are methods to reduce manufacturing costs like using non-viral vectors. Exciting approaches are currently being developed to increase the effectiveness and scope of CAR-T-cell therapies while improving safety and enabling efficient production of these agents. These promising technical solutions to optimize CAR T-cell therapy will lead to the adoption of this technology for wider application in cancer therapy and to expand the benefits of CAR T-cells to patients. The discovery of CAR T-cell therapy is a step towards eradicating cancer but more research needs to be done to accelerate the effectiveness and reduce the cost of the therapy [28, 31].

XII. ABBREVIATIONS

CAR	Chimeric antigen receptors
TAA	Tumor associated antigens
ITAM	Immunoreceptor tyrosine-based activation motifs
ACT	Adoptive T cell therapy
ScFv	Single-chain variable fragment
IgG	Immunoglobulin G
TCR	T - cell receptor
CD	Cluster of Differentiation
CM	Costimulatory molecule
IS	Immune synapse
CNS	Central nervous system
MHC	Major histocompatibility complex
IL	Interleukin
BLA	Biologics license application
FDA	Food and Drug Administration
EMA	European Medicines Agency
DLBCL	Diffuse large B-cell lymphoma
PMBCL	Primary mediastinal large B-cell lymphoma

ALL	Acute lymphoblastic leukaemia
ODAC	Oncologic Drugs Advisory Committee
MRD	Minimal residual disease
CR	Complete remission
CRi	Count recovery
CRS	Cytokine release syndrome
HSCT	Hematopoietic stem cell transplantation
ICANS	Immune effector cell-Associated Neurotoxicity Syndrome
TGF-β	Transformation in the growth factor-β
GMOs	Genetically modified organisms
HSPG	Heparan sulfate proteoglycans
CMS	Centers for Medicare and Medical Services
GMPs	Good manufacturing practices
ORR	Objective Response Rate

REFERENCES

[1] Mohanty, R., Chowdhury, C. R., Arega, S., Sen, P., Ganguly, P., & Ganguly, N. (2019). CAR T cell therapy: a new era for cancer treatment. *Oncology reports*, *42*(6), 2183-2195.

[2] Sharpe, M., & Mount, N. (2015). Genetically modified T cells in cancer therapy: opportunities and challenges. *Disease models & mechanisms*, *8*(4), 337-350.

[3] McGuirk, J., Waller, E. K., Qayed, M., Abhyankar, S., Ericson, S., Holman, P., ... & Myers, G. D. (2017). Building blocks for institutional preparation of CTL019 delivery. *Cytotherapy*, *19*(9), 1015-1024.

[4] Zhang, C., Liu, J., Zhong, J. F., & Zhang, X. (2017). Engineering car-t cells. *Biomarker research*, *5*(1), 1-6.

[5] Chu, F., Cao, J., & Neelalpu, S. S. (2018). Versatile CAR T-cells for cancer immunotherapy. *Contemporary Oncology*, *22*(1A), 73.

[6] Li, J., Li, W., Huang, K., Zhang, Y., Kupfer, G., & Zhao, Q. (2018). Chimeric antigen receptor T cell (CAR-T) immunotherapy for solid tumors: lessons learned and strategies for moving forward. *Journal of hematology & oncology*, *11*(1), 1-18.

[7] Benmebarek, M. R., Karches, C. H., Cadilha, B. L., Lesch, S., Endres, S., & Kobold, S. (2019). Killing mechanisms of chimeric antigen receptor (CAR) T cells. International journal of molecular sciences, 20(6), 1283.

[8] Mayo Clinic. (2017). Non-Hodgkin's lymphoma. www.mayoclinic.org/diseases-conditions/non-hodgkins-lymphoma/symptoms-causes/syc-20375680.

[9] National Cancer Institute. (2017). SEER cancer stat facts: non-Hodgkin lymphoma. https://seer.cancer.gov/statfacts/html/nhl.html.

[10] Neelapu, S. S., Locke, F. L., Bartlett, N. L., Lekakis, L. J., Miklos, D. B., Jacobson, C. A., ... & Go, W. Y. (2017). Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *New England Journal of Medicine*, *377*(26), 2531-2544.

[11] US Food and Drug Administration. (2017). FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma: Yescarta is the second gene therapy product approved in the U.S. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm.

[12] US Food and Drug Administration. (2017). YESCARTA™(axicabtagene ciloleucel) suspension for intravenous infusion. *FDA https://www. fda. gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226. pdf*.

[13] okays second CAr-t, F. D. A. for Kite.

[14] Kymriah™ (tisagenlecleucel) for Acute Lymphoblastic Leukaemia (clinicaltrialsarena.com)

[15] US Food and Drug Administration. (2020). FDA approves brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma. FDA approves brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma | FDA.

[16] Hartmann, J., Schüßler-Lenz, M., Bondanza, A., & Buchholz, C. J. (2017). Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts. *EMBO molecular medicine*, *9*(9), 1183-1197.

[17] Brown, C. E., & Mackall, C. L. (2019). CAR T cell therapy: inroads to response and resistance. *Nature Reviews Immunology*, *19*(2), 73-74.

[18] Hay, K. A., Gauthier, J., Hirayama, A. V., Voutsinas, J. M., Wu, Q., Li, D., ... & Turtle, C. J. (2019). Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. *Blood*, *133*(15), 1652-1663.

[19] Sommermeyer, D., Hudecek, M., Kosasih, P. L., Gogishvili, T., Maloney, D. G., Turtle, C. J., & Riddell, S. R. (2016). Chimeric antigen receptor-modified T cells derived from defined CD8+ and CD4+ subsets confer superior antitumor reactivity in vivo. *Leukemia*, *30*(2), 492-500.

[20] Guest, R. D., Hawkins, R. E., Kirillova, N., Cheadle, E. J., Arnold, J., O'Neill, A., ... & Gilham, D. E. (2005). The role of extracellular spacer regions in the optimal design of chimeric immune receptors: evaluation of four different scFvs and antigens. *Journal of immunotherapy*, *28*(3), 203-211.

[21] Hudecek, M., Sommermeyer, D., Kosasih, P. L., Silva-Benedict, A., Liu, L., Rader, C., ... & Riddell, S. R. (2015). The nonsignaling extracellular spacer domain of chimeric antigen receptors is decisive for in vivo antitumor activity. *Cancer immunology research*, *3*(2), 125-135.

[22] Li, Y., & Kurlander, R. J. (2010). Comparison of anti-CD3 and anti-CD28-coated beads with soluble anti-CD3 for expanding human T cells: differing impact on CD8 T cell phenotype and responsiveness to restimulation. *Journal of translational medicine*, *8*(1), 1-15.

[23] Kravets, V. G., Zhang, Y., & Sun, H. (2017). Chimeric-antigen-receptor (CAR) T cells and the factors influencing their therapeutic efficacy. *Journal of immunology research and therapy*, *2*(1), 100.

[24] Gust, J., Hay, K. A., Hanafi, L. A., Li, D., Myerson, D., Gonzalez-Cuyar, L. F., ... & Turtle, C. J. (2017). Endothelial activation and blood–brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer discovery*, *7*(12), 1404-1419.

[25] Neelapu, S. S., Tummala, S., Kebriaei, P., Wierda, W., Gutierrez, C., Locke, F. L., ... & Shpall, E. J. (2018). Chimeric antigen receptor T-cell therapy—assessment and management of toxicities. *Nature reviews Clinical oncology*, *15*(1), 47.

[26] American Cancer Society. (2021). CAR T-cell Therapy and Its Side Effects.

[27] Zhang, E., Gu, J., & Xu, H. (2018). Prospects for chimeric antigen receptor-modified T cell therapy for solid tumors. *Molecular cancer*, *17*(1), 1-12.

[28] Rafiq, S., Hackett, C. S., & Brentjens, R. J. (2020). Engineering strategies to overcome the current roadblocks in CAR T cell therapy. *Nature reviews Clinical oncology*, *17*(3), 147-167.

[29] Zhang, E., & Xu, H. (2017). A new insight in chimeric antigen receptor-engineered T cells for cancer immunotherapy. *Journal of hematology & oncology*, *10*(1), 1-11.

[30] Graham, C., Hewitson, R., Pagliuca, A., & Benjamin, R. (2018). Cancer immunotherapy with CAR-T cells–behold the future. *Clinical Medicine*, *18*(4), 324.

[31] Marofi, F., Motavalli, R., Safonov, V. A., Thangavelu, L., Yumashev, A. V., Alexander, M., ... & Khiavi, F. M. (2021). CAR T cells in solid tumors: challenges and opportunities. *Stem cell research & therapy*, *12*(1), 1-16.

[32] Zhang, B. L., Qin, D. Y., Mo, Z. M., Li, Y., Wei, W., Wang, Y. S., ... & Wei, Y. Q. (2016). Hurdles of CAR-T cell-based cancer immunotherapy directed against solid tumors. *Science China Life Sciences*, *59*(4), 340-348.

[33] June, C. H., O'Connor, R. S., Kawalekar, O. U., Ghassemi, S., & Milone, M. C. (2018). CAR T cell immunotherapy for human cancer. *Science*, *359*(6382), 1361-1365.

[34] Prasad, V. (2018). Tisagenlecleucel—the first approved CAR-T-cell therapy: implications for payers and policy makers. *Nature Reviews Clinical Oncology*, *15*(1), 11-12.

[35] Wang, X., & Rivière, I. (2016). Clinical manufacturing of CAR T cells: foundation of a promising therapy. *Molecular Therapy-Oncolytics*, *3*, 16015.

[36] Fritsche, E., Volk, H. D., Reinke, P., & Abou-El-Enein, M. (2020). Toward an optimized process for clinical manufacturing of CAR-Treg cell therapy. *Trends in biotechnology*.

[37] U.S. Food and Drug Administration. (2021). FDA approves idecabtagene vicleucel for multiple myeloma. FDA approves idecabtagene vicleucel for multiple myeloma | FDA.

[38] U.S. Food and Drug Administration. (2021). FDA Approves New Treatment For Adults With Relapsed Or Refractory Large-B-Cell Lymphoma. FDA Approves New Treatment For Adults With Relapsed Or Refractory Large-B-Cell Lymphoma | FDA.