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Review Article

CHIMERIC ANTIGEN RECEPTOR T CELLS: PAST, PRESENT, AND FUTURE

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ABSTRACT

Chimeric antigen receptor T (CAR T) therapy, a type of anticancer cellular immunotherapy, is emerging expeditiously. Primarily reported in 1987, the concept of a chimeric T-cell receptor (TCR), which combines antibody-derived variable regions with TCR-derived constant regions, was then, followed by double-chain chimeric TCR (cTCR) and single-chain variable fragment receptor chimeric cell (referred to as "T-bodies," the prototypes of modern CAR). The CAR construct, which incorporates both a costimulatory endodomain and the CD3ζ signaling endodomain, is classified as a second-generation CAR, and this later achieved fantastic success in human clinical trials, marking a momentous milestone in the development journey of the CAR T-cell therapy. Tisagenlecleucel was the first CAR T-cell therapy to be approved by the Food and Drug Administration (FDA) for treating pediatric and young adult acute lymphoblastic leukemia. Six CAR T-cell therapies have been approved by FDA; many more are still there in the budding stages. The major challenges for CAR T-cell therapy are safety, ineffectiveness for solid tumors, cost, etc. To overcome these elements, further research is essential.

Keywords: CAR T-cell therapy, Chimeric antigen receptor T cells, Anticancer therapy, Autologous T cells, Living drug

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INTRODUCTION

Right now, without any doubt, cancer is the most significant contributor to disability-adjusted life years and the second highest cause of worldwide mortality [1-3]. For decades, the foundations of cancer treatment were surgery; chemotherapy, and radiation therapy, still recently newer treatments like immunotherapy have transformed cancer treatment, offering a beacon of hope to once-desperate patients with late-stage metastatic cancers [4-6]. Immunotherapy encompasses a broad spectrum of treatments designed to induce, augment, or suppress the immune response, that fine-tune the immune system to strike a balance between eliminating harmful pathogens and protecting normal body tissues from the collateral damage of an inflammatory response. Monoclonal therapeutic antibodies, immune checkpoint inhibitors, cytokines, and immunomodulators are methods to mediate the immune response [7-12].

Chimeric antigen receptor T (CAR T) therapy, the most rapidly developing branch of anticancer cellular immunotherapy, already accounts for >50% of the cell therapies that are under development for hematological malignancies. As of March 2020, there were 1483 anticancer cell therapies under research or on the market worldwide, with an increase of 46.7% compared with 1011 in 2019. Among these, 858 were CAR T-cell therapies in 2020, a rise of more than 50% compared to the corresponding quarter last year [13,14].

In CAR T-cell therapy, autologous T cells are isolated from the patient's blood, genetically modified with enhanced specificity and killing efficacy toward the patient's cancer cells. Then, they are reinjected into the host to help clear the tumor. This is accomplished through genetic modification of the T cells to express the CAR, a receptor engineered to recognize a given antigen of the patient's cancer cells and subsequently activate the CAR T cells' expansion and cytotoxic potential [3,17,18,19].

HISTORY OF CAR T-CELL THERAPY

The concept of a chimeric T-cell receptor (TCR), which combines antibody-derived variable regions with TCR-derived constant regions, was first reported in 1987, by a Japanese immunologist Dr. Yoshikazu Kurosawa and team. He suggested that, in response to antigens, the chimeric receptor could activate T cells [6,20]. Two years later, in 1989, Israeli immunologist Dr. Zelig Eshhar and his colleagues described a similar approach to redirect T cells to recognize antigens in a non-major histocompatibility complex (MHC)-restricted manner. The chimeric TCR (cTCR), thus developed, was comprised of anti-2,4,6-trinitrophenyl (TNP) antibody Sp6's variable heavy and light chains which were fused with constant regions of α and β TCR chains, respectively. The functional cTCRs are expressed on cell surface, and they can bind to TNP antigen on co-transfection into murine MD.45 cytotoxic T lymphocyte hybridoma cells, leading to T-cell activation, as evidenced by interleukin-2 (IL-2) production and the killing of target cells. The MHC-independent activation of cTCR-expressing T lymphocytes was demonstrated further by IL-2 production on binding to TNP-coupled proteins adsorbed onto a plastic substrate [6,15,21].

The double-chain heterodimeric cTCRs had low cotransduction efficiency as it required infecting T cells with two separate retroviral vectors. To overcome this low cotransduction efficiency, Dr. Eshhar's team designed a single-chain chimeric receptor in which the single-chain variable fragment (scFv) was fused to a lymphocyte intracellular signaling domain from either CD3ζ or FcεRIγ, resulting in the first-generation CAR, single-chain variable fragment receptor (scFvR). The scFv antigen-binding domain was derived from a monoclonal antibody, and it retained the antigen-binding affinity and specificity of its parental antibody. When expressed in MD.45 T-cell hybridoma cells, the scFvR conferred non-MHC-restricted activation on antigen exposure. Compared to cTCR, the scFvR had increased vector transduction efficiency and could independently transduce the T-cell activation signal, bypassing the need for the conventional TCR complex. The double-chain cTCR and the single-chain scFvR were referred to as "T-bodies" and are the prototypes of modern CAR [6,22-33].

Typically, T-cell activation requires two signals: The first one is triggered by the engagement of the TCR with peptide-loaded MHC, and the second one is provided by costimulatory receptors

like CD28 [6,35]. It was therefore suggested that incorporating a costimulatory endodomain into engineered T cells could enhance their proliferation and persistence. Dr. Michel Sadelain designed a chimeric receptor that combined the CD3ζ and CD28 endodomains, which provided both activation and costimulatory signals and led to enhanced antigen-dependent proliferation, IL-2 production, and cancer cell killing. T-cells expressing chimeric receptors containing both CD3ζ and CD28 endodomains showed significantly increased expansion and persistence compared to T-cells expressing chimeric receptors containing only the CD3ζ endodomain in human patients [6,36-38]. Dr. Dario Campana incorporated the 4-1BB/CD137 signal transduction domain in the CAR design which significantly improved the persistence and antitumor activity of CAR-engineered T cells. The CAR construct that contained both a costimulatory endodomain and the CD3ζ signaling endodomain was classified as a second-generation CAR and later achieved remarkable success in human clinical trials, marking a momentous milestone in the journey of developing CAR T-cell therapy [6,39,40]. Fig. 1 outlines the key milestones in the field of CAR T-cell therapy.

CAR T-CELL THERAPY: THE MAKING OF THE "LIVING DRUG"

According to Dr. Renier J. Brentjens, an early leader in the field, CAR T-cell therapy is equivalent to "giving patients a living drug." The backbone of CAR T-cell therapy is T cells which help to organize the immune response, thus directly killing the cells infected by pathogens. CAR T-cell therapies are customized for individual patients; they are made by means of collecting T cells from patients and re-engineering them in the laboratories to produce proteins on their surface, which are known as CARs. The CARs recognize and bind to the specific proteins on the surface of cancer cells (Antigens). After these revamped T cells are "expanded" into the millions in the laboratory, they are then infused

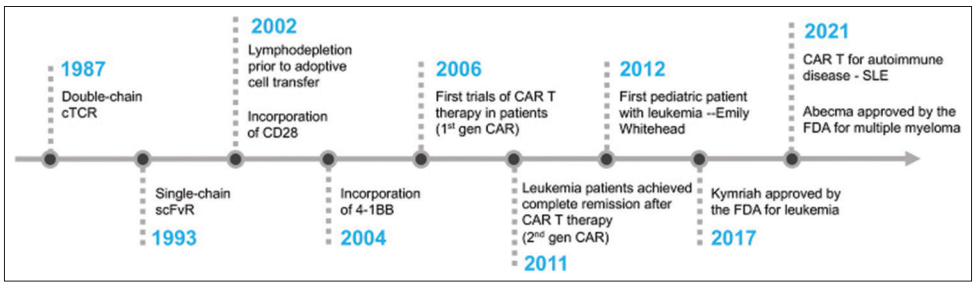

Fig. 1: Key milestones in the development of chimeric antigen receptor T-cell therapy [6]

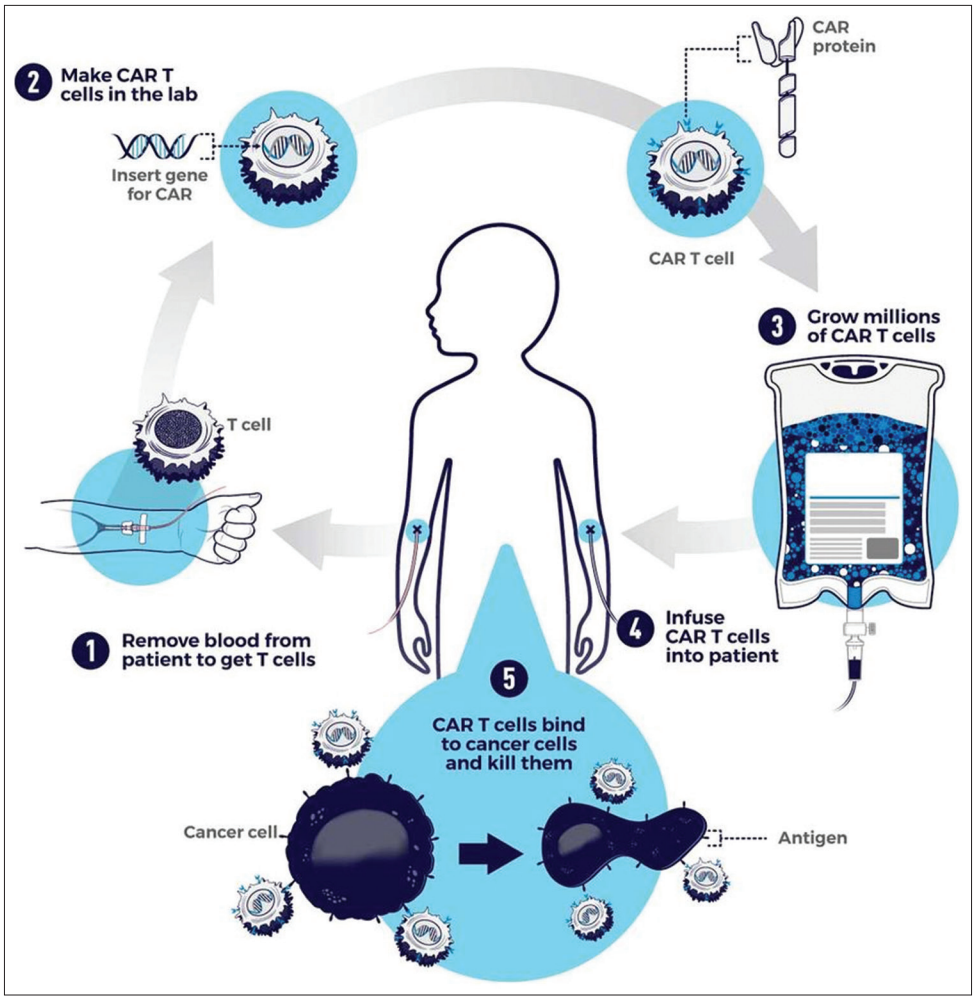

Fig. 2: Chimeric antigen receptor T-cell therapy [16]

back into the patient. In the patient's body, CAR T cells will continue to multiply and, under the direction of their engineered receptor, recognize and destroy any cancer cells that accommodate the target antigen on their surfaces (Fig. 2) [41].

THE CLINICAL SUCCESS STORY OF CAR T-CELL THERAPY

The second-generation CAR T-cell therapy demonstrated effectiveness in one patient with advanced follicular lymphoma, and in patients with refractory chronic lymphocytic leukemia (CLL) and relapsed B-cell acute lymphoblastic leukemia (ALL). The therapy for advanced follicular lymphoma involved using a retroviral vector called MSGV to express a CD19-specific CAR. This CAR was designed to target the protein found on the surface of B-cells called CD19 using an anti-CD19 scFv derived from FMC63 murine monoclonal antibody. It has both a CD28 costimulatory endodomain and a CD3ζ endodomain. The patient received lymphodepletion before two doses of CAR T cells and eight doses of IL-2. The patient achieved partial remission of the lymphoma and selective elimination of B-lineage cells due to this treatment. In patients with refractory CLL and relapsed B-cell ALL, autologous CD19-targeted CAR T-cells expressing the second-generation CAR (19–28z) were evaluated for their safety and persistence in treating relapsed or chemotherapy refractory CLL and B-ALL. Patients who received prior conditioning with cyclophosphamide exhibited a partial response, whereas patients treated without conditioning did not show any objective responses [6,42,43].

A critical breakthrough in CAR T-cell therapy was obtained at the University of Pennsylvania through the research of Dr. Carl June's team. They reported that three adult patients with advanced CLL achieved complete or partial remission after receiving CD19-specific CAR T-cell therapy. The CD19-CAR used in this trial contained an anti-CD19 scFv (derived from FMC63), a 4-1BB costimulatory endodomain, and a CD3ζ signaling endodomain. It was from a lentiviral vector driven by the EF1-α promoter. The CAR T-cell underwent significant expansion in patients on infusion, increasing in number by up to 1000 times. These results unlocked the potential of the second-generation CAR T-cell therapy in treating advanced CLL and other B-cell malignancies. The results of these clinical trials confirmed that prior chemotherapy to reduce the number of immune cells in the body called lymphodepletion is essential for CAR T-cell therapy to succeed. In contrast, IL-2 therapy does not seem to be necessary [44-49,62].

Tisagenlecleucel was the first CAR T-cell therapy to be approved by the Food and Drug Administration (FDA) on August 30, 2017, for the treatment of pediatric and young adult ALL. Later, three more CD19-specific CAR T cells were approved by the FDA for the treatment of different B-cell malignancies, namely, axicabtagene ciloleucel, brexucabtagene autoleucel, and lisocabtagene maraleucel. In April 2021 and February 2022, two BCMA-specific CAR T-cell therapies were approved for the treatment of multiple myeloma, namely, idecabtagene vicleucel and ciltacabtagene autoleucel [6,50-56].

Overview of Food and Drug Administration approved CAR T-cell therapies [6,40,50-65]

Molecule name	Brand name	Approval	Target Antigen	Cancer type	Study results
Tisagenlecleucel	Kymriah	August, 2017	CD19	R/R B-ALL FL LBCL	ELIANA (n=75) Overall remission rate: 81% ELARA (n=97) ORR: 86%, CR: 69% JULIET (n=93) ORR: 52%, CR: 40% BELINDA (n=162) ORR: 46%, CR: 28%
Axicabtageneciloleucel	Yescarta	October, 2017	CD19	R/R LBCL FL/MZL LBCL	ZUMA-1 (n=108) CR: 58% ZUMA-5 (n=104) ORR: 92%, CR: 74% ZUMA-7 (n=180) ORR: 83%, CR: 65%
Brexucabtagene autoleucel	Tecartus	July, 2020	CD19	R/R MCL ALL	ZUMA-2 (n=68) CR: 67% ZUMA-3 (n=71) ORR: 71%, CR: 56%
Lisocabtagene maraleucel	Breyanzi	February, 2021	CD19	R/R LBCL	Transcend NHL001 (n=269) CR: 53% TRANSFORM (n=92) ORR: 86%, CR: 6%
Idecabtagene vicleucel	Abecma	March, 2021	BCMA	R/R MM	KarMMa (n=128) CR: 33%
Ciltacabtagene autoleucel	Carvykti	February, 2022	BCMA	R/R MM	CARTITUDE-1 (n=97) CR: 82.5%

R/R: Relapsed or refractory, ALL: Acute lymphoblastic leukemia, ORR: Overall response rate, CR: Complete response rate, FL: Follicular lymphoma, LBCL: Large B-cell lymphoma, MCL: Mantle cell lymphoma, MM: Multiple myeloma, CAR T: Chimeric antigen receptor T

Overview of CAR T-cell therapies undergoing clinical trials [3,66-69]

CAR T	Cancer type	Results
CD20-targeting CARs	Various lymphomas and leukemias	Six complete remissions, three partial remissions, and two stable diseases in 11 patients in a PIICT (NCT01735604), with a median progression-free survival of 6 months.
CD22-targeting CARs	Various lymphomas and leukemias	In a PICT (NCT04088890), three patients (100%) with recurrent malignancies after CD19-targeting CAR T-cell therapy achieved complete remission. Adverse events: Grade 1 and 2 CRS and high-grade neutropenia, thrombocytopenia, and anemia
IL13Rα2-targeting CARs	Glioblastoma	A 228-day-long regression in one patient. Recurrence of cancer at four new locations, probably due to reduced TAA expression. (PICT NCT02208362).
Allogeneic NKG2D-based CAR (CYAD-101)	Metastatic colorectal cancer	In this PICT (NCT03692429) (n=15), two partial responses and nine stable diseases were achieved, 7 of which lasted at least 3 months. Median progression-free survival: 3.9 months.
HER2-targeting CARs	HER2+cancers (pancreatic, breast, gastric, others)	In an advanced pancreatic cancer, PICT (NCT01935843) of 11 patients, a 4.5-month-long partial response and five stable diseases were achieved. Median progression-free survival of 4.8 months (range, 1.5–8.3 months).
GPC3-targeting CARs	Hepatocellular carcinoma	In two advanced hepatocellular carcinoma PICTs (NCT02395250 and NCT03146234), of a total of 13 patients, two partial responses were obtained. One patient with stable disease was alive after 44.2 months. Overall survival of 50.3% (6 months) and 10.5% (3 years). One Grade 5 and several Grade 1/2 CRS events were recorded.

CRS: Cytokine-release syndrome; PICT: Phase I clinical trial; PIICT: Phase II clinical trial, CAR T: Chimeric antigen receptor T, HER2: Human epidermal growth factor receptor 2

MAJOR CHALLENGES IN CAR T-CELL THERAPY

CAR T-cell therapies have shown outstanding results, but their limitations are coming to light with an extensive research [3,6].

Tumor-antigen escape

Refractory cancer subclones often overtake tumors due to the highly selective nature of the targeted therapy. For example, in large B-cell lymphoma patients, anti-CD19 CAR T-cells effectively eliminate most of the CD19+ cancer cells; however, CD19− cancer cells escape the targeted therapy and can then increase at will and perpetuate the cancer [3,19,70,71].

Ineffectiveness against solid tumors

Despite the remarkable success and revolutionary impact of CAR T-cell therapy on the treatment of hematological cancers, the same is not the case for solid cancers. Multiple reasons, including immunosuppressive tumor microenvironment and lack of tumor-exclusive target, are there for the impaired reach and effectiveness of CAR T cells in solid cancers [3,72-78].

CAR T cells are to be infused into the blood, and they must then travel to the region where the tumor is located; this is a process dependent on chemokine attraction signals and therefore varies from tumor to tumor. On reaching the tumor site, the lymphocytes must penetrate through the layers of extracellular matrix (ECM) which is frequently thickened and stiffened by intense collagen and heparan sulfate proteoglycan deposition carried out by tumor-associated fibroblasts. T cells do not form substantial amounts of ECM-degrading enzymes, and this barrier deeply hinders the accessibility of CAR T cells to their target cells. Microenvironment of solid tumors is often oxidative, hypoxic, acidic, and nutrient-starved, and consists of high amounts of immunosuppressive elements or even the tumor cells themselves. This immunologically deleterious "cold tumor" environment encourages the development of anergic and apoptotic states in the CAR T cells [3,34,72-78].

It is challenging to find tumor-associated antigens (TAAs) that are specifically yet uniformly expressed at high levels in the tumor. TAAs are generally present at higher expression in cancer cells; still they are also co-expressed at shallow levels in non-malignant tissues, enabling dangerous cross-reactivity and on-target off-tumor toxicity. Even when dealing with TAAs of very low expression in healthy cells, solid tumors are usually very heterogeneous, so wide antigen expression variability and antigen-loss events are pretty common [3,72-78].

Cytokine-release syndrome (CRS)

CRS is a type of cytokine storm syndrome, graded between I and IV depending on symptomatic severity, caused by exaggerated levels of circulating inflammatory cytokines, such as IL-6 and IFN-γ. Mild cases often present with flu-like symptoms and systemic inflammatory response symptoms such as fever, fatigue, and generalized pain. Severe cases display features like hypotension as well as high fever, and it can progress to an uncontrolled systemic inflammatory response with circulatory shock needing vasopressor, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure. This requires medical attention that is imperative, and sometimes it can escalate to patient's death. Clinical trials of anti-CD19 CAR T cells in blood cancers have often reported high frequencies of CRS, sometimes as high as 100%, and related fatalities. An apparent connection between tumor burden and severity of CRS reactions has been reported several times regarding CAR T-cell treatments [3,79-82].

Neurotoxicity

Adverse CAR T-cell-induced neurotoxicity, also known as immune effector cell-associated neurotoxicity (ICANS), is reported to occur in approximately two-thirds of leukemia and lymphoma patients who are treated with adoptive CAR T-cell transfer. Although its pathophysiology is still ambiguous, general clinical understanding states that exacerbated immune activation and elevated serum and cerebrospinal fluid cytokines play an essential role in blood-brain barrier dysfunction and neurotoxicity. Clinically, ICANS can present itself through expressive aphasia, tremor, dysgraphia, and lethargy; these symptoms can progress to global aphasia, seizures, obtundation, stupor, and coma and often follow or occur concomitantly with events of CRS [3,81-84].

On-target off-tumor toxicity

It occurs when the cognate antigen of the CAR T cells is expressed not only in the targeted tumor cells but also in normal cells. As the potent, genetically modified T lymphocytes travel through the blood and infiltrate the various body tissues, they encounter all types of cells; (1) normal cells, with no expression of the specific antigen, that go by immunologically invisible, (2) target malignant cells, which highly express the antigen and are therefore attacked by the lymphocytes, (3) problematic, target antigen-negative malignant cells, which often escape unscathed from the cytolytic action of CAR T cells, and (4) normal cells expressing the target antigen, which then get caught in the immune crossfire and end up succumbing to the inflammatory and cytolytic action of the CAR T cells. This "friendly fire" can have serious consequences, damaging healthy tissue and compromising its function, besides creating unnecessary inflammation, which can have detrimental effects both locally and systemically [3,85,86].

FUTURE PERSPECTIVES

The outstanding achievement of CAR T-cell therapy has inspired scientists to research the potential of engineering other immune cells, such as Natural Killer (NK) cells, NKT cells, macrophages, and neutrophils, for therapeutic purposes. Among these, CAR-NK cell therapy has shown magnificent responses in human clinical trials. These immune cells have fewer concerns of graft-vs-host disease, making them more suitable as off-the-shelf products; still they also have their limitations, such as limited proliferation capabilities, short life spans, and inability to form memory cells. T cells can be genetically engineered to target tumors through tumor-neoantigen-specific TCRs. This therapy has a significant advantage as the target is not limited to membrane antigens [87-92].

In conclusion, CAR T-cell therapy has made remarkable progress in the treatment of cancer, but there are several challenges to make this treatment widely available and effective. Further research in the development of CAR T-cell therapy for solid tumors, off-the-shelf CAR T-cell therapy, safety, cost, and non-cancer diseases will be crucial to the future success of this treatment. The progress made in CAR T-cell therapy calls for the importance of continued investment in scientific research and innovation.

CONFLICTS OF INTEREST

None.

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