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REVIEW ARTICLE

Car-T Cell Therapy for Cancer: A Review

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ABSTRACT
CAR-T cell therapy is becoming gamechanger in treating of various types of cancer. However, this treatment has produced extraordinary clinical responses in cancer patients but the treatment expected and unexpected toxicities are generated. Avoiding the toxicity has become a crucial step in the thriving application of this happening technology. In this review we discussed about the FDA approved CAR-T cell therapies and the toxicities including cytokine release syndrome, neurological toxicity.
Key Words: *CAR-T, Cancer, Tisagenlecleucel.*

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INTRODUCTION

Cancer is described as aberrant activation of various cell cycle proteins, which leads in uncontrolled cell proliferation. Cell-based immunotherapies have been chosen as front-line cancer treatment options. To combat cancer, many techniques such as monoclonal antibodies (mAbs), tumour vaccines, immune checkpoint blockades, cytokine-induced killers (CIKs), bispecific antibodies, tumour-infiltrating lymphocytes (TIL), and chimeric antigen receptor T (CAR-T) have been used[1] CAR T-cell therapy is a "precision medicine" treatment, which means it is tailored to each patient. Zelig Eshhar and colleagues first proposed the concept of the chimeric antigen receptor (CAR; also known as T-cell bodies or chimeric immunological receptors) about 15 years ago [2] .Adoptive T cell transfer (ACT) using advanced ex vivo culture and cellular engineering methodologies has resulted in long-term therapeutic responses in previously treatment-refractory patients. Recently, tumours have been discovered, indicating ACT's strength and potential. The limits of currently available medicines in inducing remissions reliably and sustainably in patients with advanced, relapsing, or resistant cancers have helps us focus in immunotherapy, particularly antibody-based and adoptive cellular therapies [3]. CAR-T cell therapy marks a new era in cancer immunotherapy. The ability of genetic engineering to alter the genome and induce specificity of T-cells against cancer cells in the form of chimeric antigen receptor is a huge success in cancer treatment. It is a type of adoptive cell transfer (ACT). Preliminary studies using such cells have been encouraging. CAR T cells are at the frontline of cell-based treatments for cancer treatment. In clinical studies for individuals with chronic lymphocytic leukaemia (CLL) and acute lymphocytic leukaemia (ALL), CAR-T cells targeted to CD19 have demonstrated exceptional results. CAR-T-cell attachment to target cells after antigen identification results in target cell death and the releasing of effector cytokines IFNg, IL2, and TNF. In addition, preclinical investigations have shown that perforin and Granzyme B are essential for CAR-T cell effectiveness in vivo [4] . B-cell tumours that express many TAAs unique to B cells, such as CD19, CD20, CD22, CD23 and CD38, may be ideal targets for these immunotherapeutic methods. In a single fusion molecule, the CAR method combines the antigen specificity of an antibody with the capability of T cells to promote tumour cell death. Moreover, CAR-modified T cells actively and selectively home to tumour locations and remain in vivo as memory cells. As a result, CAR-modified T cells aimed towards TAAs may be more potent than mAbs in activating long-lasting tumour responses [5],[6] .The CD19 chimeric antigen receptor (CAR) therapy has quickly had a significant impact in oncology after a decade of preclinical

research. The CAR field has advanced in recent years from early reports of anecdotal responses in patients with non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukaemia (CLL) to achieving reproducible outcomes in hundreds of patients with B cell malignancies, most notably in B cell acute lymphoblastic leukaemia [7]. Patients still die from relapsed/refractory (R/R) disease even though B-cell non-Hodgkin lymphomas (NHLs) are usually highly sensitive to chemotherapy and immunotherapy. The last significant development for the two most prevalent subtypes, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, happened more than 20 years ago with the approval of the CD20 mAb rituximab. Novel examples like, Lenalidomide, bortezomib, and ibrutinib are more focused medications that have been used in frontline treatments, but many clinical trials have failed to present their superiority. The variable portions of the heavy and light chains from an antibody that linked to 2,4,6-trinitrophenyl were stitched onto the constant domains of the and chains of the T cell receptor in 1989, resulting in the creation of the first real CAR T cell [8].

HISTORY

Animal research models, as is often the case, acted as the foundation for the concept of adoptive cellular treatment for tumour allografts. Researchers first proved that an allogeneic haematopoietic graft was essential for eliminating leukaemia following transplantation in mice. The clinical strategy of allogeneic bone marrow transplant is based on the notion that the graft itself has anti-leukaemia capabilities. This concept was further strengthened by the key observation of Weiden et al (1979) that haematopoietic stem cell transplantation using allogeneic donors was more effective than use of syngeneic donors in avoiding leukaemia relapse. As a result, allogeneic T cells are likely to recognise targets on leukaemia cells that syngeneic T cells cannot. Researchers expanded on this basis, looking for strategies to get autologous lymphocytes to recognise leukaemia cells in order to fulfil the promise of efficacy while avoiding the toxicity of graft-versus-host disease (GvHD). Many lessons were acquired in early adoptive cell therapy experiments, most notably that the crucial variables were the antibody fragment's target, the differentiation status of the cells to be transferred, and the host environment [9], [10].

Structure of CAR-T cell:

These cells consist of Endo domain, transmembrane domain, ectodomain.

Ectodomain: The domain which is membrane protein present outside the cytoplasm and this ectodomain is made-up of antigen recognition region, signal peptide and spacer.

Transmembrane domain: This is the most proximate component to the Endo domain consisting of lipid bilayer which traverse the membrane. The stability of the receptor will depend upon this domain. CD28 is commonly used when compared to CD3-zeta because CD28 is most stable than others.

Endodomain: This is the end region of the receptor which consists of stimulatory (CD3 ζ) co-stimulatory molecules (CD27, CD28, ICOS, 4-1BB, OX40) [11].

Genetically Targeted T Cells: Chimeric Antigen Receptors

To target tumour-associated antigens, autologous T lymphocytes can be genetically engineered (TAA). Gene transfer of cloning T-cell receptors (TCRs) produced from tumour antigen-specific T-cell clones is one method of genetically altering T cells to target specific TAA. This strategy has been demonstrated to be feasible in clinical studies of metastatic melanoma, although published data applying this strategy in the setting of B-cell cancers is restricted. Adoptive transfer of Chimeric Antigen Receptor T-cells (CAR-Ts) has emerged as a strong promising immunotherapeutic technique for the treatment of B-cell malignancies, and the technique's extraordinary adaptability makes it potentially applicable to a wide spectrum of human diseases.

Design Of Chimeric Antigen Receptor:

CARs are recombinant proteins made up of an intracellular signalling domain coupled to a hinge or spacer and an antigen recognition domain, most frequently a single chain variable fragment (scFv). There have been several CAR iterations created and evaluated in the lab and in the clinic. The first-generation CAR prototype arrangement delivers a T-cell receptors (TCR)-like "signal 1" exclusively, generally via CD3 or Fcer1. However, in pre-clinical and clinical trials, there was insufficient T-cell growth, persistence, and anti-tumour activity, which resulted in further CAR design adjustments. The first-generation CAR prototype design delivers a T-cell receptors (TCR)-like "signal 1" exclusively, generally via CD3 or Fcr1. However, in pre-clinical and clinical trials, there was insufficient T-cell growth, persistence, and anti-tumour activity, which resulted in further CAR design adjustments. Following clinical development, second generation CARs have shown their revolutionary potential. In order to integrate signals 1 and 2, this alteration involved adding a single intracellular costimulatory module above CD3. Costimulatory receptors like CD28 and 4-1BB encourage increased interleukin-2 (IL-2) release and T-cell proliferation when they are included into a linear CAR design. In third-generation CAR designs, two or more costimulatory domains, such as CD28,

4-1BB, OX40, or ICOS, are combined. The third generation CAR platform's superiority is supported by minimal clinical evidence, and the technology's actual enabling is still in issue[12], [13] .

CAR T cells in NHL:

Most NHL cases are diffuse large B-cell lymphoma (DLBCL). While many patients recover from front-line treatment, 10% to 15% of patients show refractory disease by 3 months after starting treatment, and 20% to 35% will relapse[14]. Chemotherapy combined with autologous HSCT is second-line therapy for patients who are not in remission, with a Progression free survive (PFS) of 30% to 40% three years after HSCT. When relapses happen after an autologous transplant, allogenic HSCT may be considered. A median OS of 4.4 months is the prognosis for those who cannot obtain HSCT. Therefore, research into CAR T-cell therapy for DLBCL and other mature B-cell lymphomas is clearly needed, and efforts in this field were made simultaneously with research into CAR T cells for Acute lymphoblastic leukaemia ALL [15], [16].

Alternative target antigens in B-malignancies:

CD19 is an excellent target for CAR T cells since it is expressed evenly at high site density on B-cell tumours and is not eliminated as a soluble molecule. Therefore, targeting a specific antigen in cancer raises the risk of antigen loss variants developing. Surface immunoglobulin light chain, CD20, and CD22 are some of the cell-surface molecules on B-cell malignancies that have been targeted using CAR T cells. (4(21)). The first alternative to and salvage therapy after CD19 CAR T cells for B-Acute lymphoblastic leukaemia (B-ALL) is the CD22 CAR T-cell design. It provides a choice for CD19-negative relapse that is seen after either CD19 CAR T cells or blinatumomab and broadens treatment choices for mature B-cell lymphomas [17].

Transduction for CAR-T cells:

A tool is required to deliver the foreign gene into human cells. Gene incorporation is performed by two ways with vectors, i.e., viral systems and non-viral systems. Viruses are considered as the major vectors which are used in basic research and clinical study, as of the high transfer efficiency, moderately short time required to gain the clinically necessary amount of cultured T cells and the possibility of different expression characteristics. The majority of viral systems may accept genes from beneficial and fascinating cells as well as offer the viral structural enzymes and proteins necessary for the production of infectious viral particles that include vectors. Adenovirus, adeno-associated virus, and retroviruses (including lentivirus) are some of the virus vectors. Among these, genetically modified retroviruses are the most widely used tools for gene delivery. A family of retroviruses is called Retroviridae. Differences within this family include pathogenicity, host range, genome structure, and amino acid and nucleotide sequence. The virus vectors, however, could be harmful. The carrier capacity is restricted, and the titer obtained is not enough, and the insertion mutation employed to elicit the immune response has the potential to cause cancer and toxicity [18] .

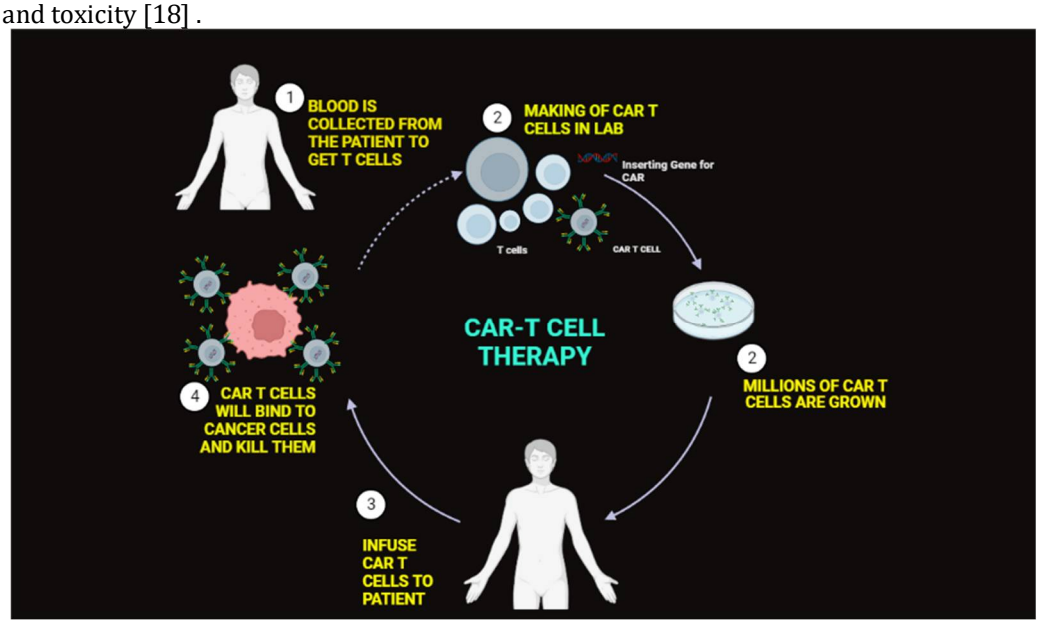

Figure 1: Production of CAR T cells

CAR -T therapies approved by FDA:

S.L. Maude et.al., studied Tisagenlecleucel by infusing to 75 patients as part of a planned analysis so that their efficacy could be assessed. All patients who responded to treatment were found to have minimal residual illness that was undetectable by flow cytometry, resulting in an overall 3-month remission rate of

81%. They failed to reach the median time in remission. For up to 20 months, Tisagenlecleucel was shown to remain in the blood. In 73% of patients have been identified Tisagenlecleucel related adverse events. CRS (cytokine release syndrome) was experienced by 77% of patients, 48% of patients who received tocilizumab [19].

Stephen J. Schuster et.al., studied Tisagenlecleucel in adults by considering 93 individuals in total had an infusion and were assessed for effectiveness. There were 14 months between the injection and data cut-off on average (range, 0.1 to 26). The highest overall response rate was 52% (95% confidence interval, 41 to 62), with complete responses coming from 40% of the patients and partial responses from 12%. Across prognostic groupings, response rates were comparable. The probability of relapse-free survival was expected to be 65% at 12 months following the initial response. The adverse events grade 3 and grade 4 are commonly seen which includes cytokine release syndrome, cytopenia, febrile neutropenia, neurological events. Within 30 days of infusion three patients from disease progression [20].

S.S. Neelapu et.al., studied Axis-cel successfully by producing for 110 (99%) and administering to 101 (91%) of the 111 individuals that were recruited. 54% of responses were complete, and 82% of responses were objective. At a median follow-up of 15.4 months, 40% of the patients still had a full response, and 42% of the patients were still responding. At 18 months, the overall survival percentage was 52%. Neutropenia (present in 78% of patients), anaemia (in 43%), and thrombocytopenia (in 38%) were the adverse events of grade 3 or higher that occurred most frequently during treatment. Neurologic events and grade 3 or higher cytokine release syndrome occurred in 13% and 28% of the patients, respectively. During treatment, three of the patients died unexpectedly [21].

Mary Kate Anderson et.al., studied about Brexucabtagene Autoleucel by administrating into patients which requires thawing at 37°C, by using of dry-thaw method or water bath. All cellular aggregates should be evenly distributed once the bag's contents have been gently stirred. Brexu-cel should be used within 30 minutes of being defrosted, although it can be kept at room temperature (20 to 25 °C) for up to 3 hours. Patients should take acetaminophen and diphenhydramine around 30 to 60 minutes before receiving a brexu-cel infusion (or another H1-antagonist). Systemic corticosteroids should not be used as a preventative measure due to their lymphotoxic effects and the potential loss of brexu-cel activity and persistence. The whole contents of the Brexu-cel bag should be infused within 30 minutes by either gravity or a peristaltic pump. The tubing should be prepared with ordinary saline prior to infusion [22].

Toxicities in CAR T cell Therapy:

Cytokine Release Syndrome:

Cytokine release syndrome mainly found in patients suffering from lymphoma and ALL treating with CAR T-cells targeting CD22, CD123 and also other T-cell therapies. This syndrome is trigged by chemokines and inflammatory cytokines released by the CAR-T cells like tumor necrosis factor, interleukin (IL-2), IL-8 and IL-10. As xenogeneic models focuses on the role of the host imune cells in the pathogenesis of the cytokine release syndrome illustrating that monocytes, dendritic cells, and macrophages are the major source of IL-6 plays vital role in causing CRS but not CAR T- cells. Lowering of macrophages and removing of monocytes will decrease the severity of CRS[23]. CRS shows symptoms assosiated with fever those are myalgia, fatigue, anorexia or rigors but can rapidly shows tachycardia, hypoxia, arrhythmia, hypotension, capillary leak, coagulopathy, respiratory failure, organ dysfunction, and shock [24]. The developing of CRS depends upon type of disease, procedure, and production related factors.

Pathophysiology of cytokine release syndrome:

The CAR T cell therapy related to mechanism of CRS can be classified into two major steps. The activation and proliferation of CAR T cells as well as the lysis of normal and tumour cells occur first as a result of the interaction between the CAR T cells and their target. This leads to the release of many cytokines, including tumor necrosis factor a (TNF-a)and interferon-g (IFN-g). In the second step, by combining these signals generates the activation monocytes and macrophages with increasing tumouricidal capacity. The progression of CRS is produced with the activated macrophages by secreting high levels of pro-inflammatory cytokines (IL-1, IL-6, IL-10), as well as other mediators which inclues nitric oxide synthase (iNOS). The endothelium and myeloid cells also appear to be significant mediators for the severity and development of CRS [25].

Hematological toxicity:

Shalev Fried et.al., studied hematological toxicity by observing 38 patients (14 children under 18yrs and 21 adults) with refractory B cell or relapsed malignancies which are enrolled on a phase 1b/2 study of locally produced CD19 CAR T cells. Patients who had relapsed or refractory B cell expressing CD19 were eligible after undergoing atleast two line of therapies.Lymphodepleting preparative regimen of fludarabine and cyclophosphamide was received by all the patients and this is followed by an intravenous infusion of

autologous CD19 CAR T cells with CD28 co-stimulatory domain. Dosing range was 1-1.5 million CAR T cells per kg [26], [27].

Neurological Toxicities:

The growing of neurologic toxicities includes delirium, expressive aphasia, obtundation, confusion, and seizure are reported in patients who received CD19 – specific CAR T cells. Although the exact pathophysiology that causes these neurologic side effects is unknown, but conciliated by expansion of supraphysiologic cytokines into the CNS or direct T cell infiltration. (Toxicity and management) Neurological symptoms are commonly resolving, but deaths only occur from cerebral oedema. It is expected that anti-CD19 CAR-Ts quickly cross the BBB and most of the treated patients are identified in the cerebrospinal fluid Neurologic events will occur within the first weeks of the treatment as similar to the CRS and considered

CRS Grade	Features of Grade	Management
Grade 1	Fever (no hypotension or hypoxia)	Diagnosis to be done to rule out infection Growth factors and antibiotics are considered if it is neutropenic IV hydration and Antipyretics
Grade 2	Fever with hypotension not requires vasopressors and hypoxia require low-flow nasal cannula	Care to be taken as in Grade 1 Supplemental oxygen and IV fluid boluses Tocilizumab +/- dexamethasone or equivalent of methylprednisolone
Grade 3	Fever with hypotension needs one vasopressor with or without vasopressin and hypoxia needs high-flow nasal cannula, non-rebreather mask, or venturi mask, facemask	Care to be taken as in Grade 1 Monitored in ICU Supplement oxygen or vasopressor support Tocilizumab + dexamethasone 10-20g given through IV q for 6hrs or its equivalent of methylprednisolone.
Grade 4	Fever with several vasopressors (apart from vasopressin) needed to treat hypotension, or hypoxia necessitating positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	Supportive care to be taken as in grade 1 Monitored in ICU Supplemental oxygen or Vasopressor support via positive pressure ventilation Tocilizumab + methylprednisolone 1000mg/day

as one of the effects of CAR-T therapy, this doesn't always predict for toxicity but some have shown a correlation [28]

Table-1: Grading and management in cytokine release syndrome

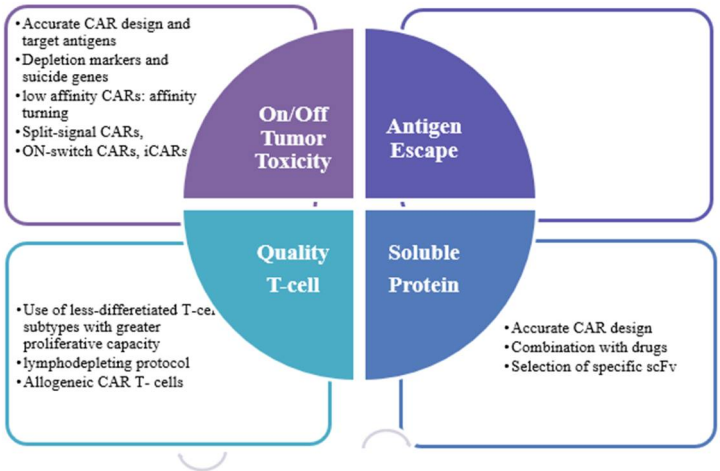

Figure 2 Current limitations in CAR-T cell therapy

CONCLUSION

Chimeric antigen receptor therapy is an outstanding therapy which is improving day-by-day in treating of various cancers like haematological cancer, ovarian cancer, lung cancer, etc., CARs are synthetic receptors consists of four major parts; one or more intracellular signalling domains, a transmembrane domain, target antigen binding domain, and extracellular target domain. CAR -T cell therapy has become the treatment for certain haematological malignancies. Though problems still exist. Further research to be made to meet the

demands of the obstacles and progressing field is challenging and needs innovative development. Selection of antigen is important for CAR T cell function. However, with appropriate antigen targeting, on-target off-tumour can cause associated toxicity. Getting CAR T cells to traffic in solid tumours and to infiltrate the tumour is challenge. Effective treatment may also lead to the risk of CAR-T cell associated toxicities like Cytokine Release Syndrome, Neurological toxicities, etc., to minimize the toxicities further studies to be performed.

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