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CRITICAL REVIEW

CARs on the road: Who gets a seat?

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ABSTRACT

Chimeric antigen receptor (CAR) T-cell therapy is a form of immunotherapy that has shown potential for inducing complete remission in relapsed/refractory hematopoietic cancers. Depending on the patient's therapeutic needs, CAR T-cells may be constructed using different cytoplasmic and extracellular domains to alter their affinity, persistence, and proliferation. While the therapy holds promise, the conventional use of CAR T-cell therapy is limited by the occurrence of side effects, substantial rates of relapse, and manufacturing logistics. The objective of this review is to discuss the potential of CAR T-cell therapies, as well as patient characteristics which may influence its efficacy.

INTRODUCTION

Engineering T-cells became commonplace in the mid-2000s, with first generation chimeric antigen receptors (CARs) developed in 1993.[1] Currently approved CAR T-cell therapies are developed from the patient's own T-cells.[2] These cells are engineered to express specific T-cell receptors targeted to an antigen on the surface of cancerous cells, allowing the immune system to identify previously unrecognizable immunomodulatory cancer cells.[2,3] CAR T-cells most commonly use a single-chain variable fragment (scFv) on the CAR to bind to cancerous antigens.[4] When this binding occurs, a signal is generated and transmitted through the CAR cytoplasmic domain, consisting of costimulatory and signalling domains, activating the CAR T-cell.[2] Once activated, the T-cells initiate cytotoxic functions which can yield cancer cell elimination.[2]

Currently, the United States Food and Drug Administration (FDA) has approved CAR T-cell therapies for the treatment of relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) and lymphomas in children and young adults.[1] Although this treatment has shown promising results, the procedure has been shown to cause adverse effects. The objective of this review is to present the benefits, challenges, and variations in success rates across demographics of patients receiving CAR T-cell therapies.

ADVANTAGES OF CAR T-CELL THERAPY

Inducing Complete Remission

CAR T-cell therapies have shown great promise for treating relapsed/refractory hematopoietic cancers by inducing complete remission in patients for whom chemotherapy is no longer effective. There are two main CAR T-cell therapies approved by the FDA: Yescarta and Kymriah.[5] The CAR T-cells used in these treatments target the CD19 antigen found on B-cell cancers like ALL and B-cell lymphomas. [6] In a clinical trial, Kymriah was administered to 93 patients with refractory B-cell lymphomas, with 52% of patients responding to the treatment and 40% achieving complete remission.[7] In a clinical trial to test the efficacy of Yescarta, 101 patients with a type of refractory lymphoma received an infusion.[8] The overall response rate after one year was 82%, out of which 58% achieved complete remission.[8] These studies demonstrate the efficacy and potential for future CAR T-cell therapies.

Reducing Off-Tumor Toxicities

One of the challenges in developing efficient cancer treatments is reducing toxicity to non-cancerous cells.[9] Many chemotherapeutic drugs target highly active pathways involved in the cell cycle that are not specific to cancer cells, thereby killing healthy cells and worsening the patient's prognosis.[10] In comparison, CAR T-cell therapies offer a degree of specificity that is absent from conventional treatments. CAR T-cells can be constructed using various scFv domains to recognize a particular antigen on cancerous cells, such as CD19 found on B-cell cancers.[11] Thus, CAR T-cell therapy has potential to significantly reduce off-tumor toxicities.

However, off-tumour toxicities are still commonplace in patients who receive CAR T-cell therapies, which requires additional treatments to manage associated adverse effects. One common example seen with CD19 CAR T-cell therapy is the ablation of B-cells, which renders the patient immunodeficient.[12] This occurs because the CD19 antigen found on hematological cancers are also found on normal B-cells.[6] These patients can be treated through periodic administration of intravenous immunoglobulins to replace the antibodies no longer being produced. Nevertheless, there are other off-tumor toxicities for which further research is needed to determine the mechanisms involved and the appropriate treatments.[12]

Variability of CAR T-Cells

Depending on the therapeutic needs of patients, CAR T-cells can be altered at the scFv and the cytoplasmic domain to modulate affinity, persistence, and proliferation.[4] Using mouse tumor models, Liu et al. observed that CAR T-cells constructed using lower affinity scFvs had fewer off-tumour responses, increasing their therapeutic index.[13] Studies suggest that high affinity scFvs may hinder CAR T-cells' ability to discriminate between cancer cells and healthy cells.[13] CD19 CAR T-cells with higher affinity scFvs for their target antigen have greater anti-tumor activity.[12]

Additionally, in a study comparing the functionality and persistence of CAR T-cell cytoplasmic domains, Zhao et al. concluded that CAR T-cells with a CD28 cytoplasmic domain expand more efficiently than those with a 4-1BB domain, leading to more rapid cytotoxic effects.[14,15] However, 4-1BB CAR T-cells demonstrate a higher persistence, generating long-term tumor immunity and reducing the risk of cancer relapse.[13,16] These two instances highlight the complex interrelationships at play in cancer immunology, complicating the development of an efficacious CAR T-cell therapy.[17]

SETBACKS IN CAR T-CELL THERAPY

Cytokine Release Syndrome

A primary adverse effect of CAR T-cell therapies is cytokine release syndrome (CRS), marked by elevated serum cytokine levels.[15] Cytokines are small proteins released by immune cells acting as chemical messengers.[18] Following their interactions with cancerous cells, activated CAR T-cells release pro-inflammatory cytokines.[15, 19] Symptoms of CRS include fever, myalgia, hypotension, and hypoxia, with severe cases resulting in hemodynamic compromise, capillary leak, arrhythmias, renal failure, and various other complications.[19] These life-threatening symptoms are also typically seen in early onset CRS, occurring within three days of CAR T-cell infusion.[15] Studies done on B-cell malignancies have shown that factors such as a high bone marrow tumor burden and higher CAR T-cell dosages pose a greater risk for developing severe CRS through rapid CAR T-cell expansion.[20,21]

The incidence and severity of adverse effects can be greatly diminished with knowledge of CRS management and early intervention. A recent study suggests that lymphoma patients over 18 years of age display a lower incidence of severe CRS compared to a population under 18 years of age.[22] In contrast, another study suggests the opposite pattern in patients with R/R ALL, where higher rates of CRS have been reported in the adult population.[23] These findings suggest a variance in the extent of CRS observed within different cancer types and a need for further research to clarify the relationship between age and CRS severity.

Immune Effector Cell-associated Neurotoxicity Syndrome

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), a form of neurotoxicity, is the second most prominent adverse effect associated with CAR T-cell therapy.[24] ICANS presents as an encephalopathy, resulting in confusion, aphasia, cerebral edema, and motor weakness, potentially leading to comas, seizures, and death.[8] The occurrence of ICANS associated with CD19 CAR T-cell therapy varies between 23-67% among patients with lymphoma, and between 40-62% in patients with leukemia.[15] As CAR T-cell therapy is a relatively novel immunotherapy, the mechanism of ICANS development is currently not well understood.[25] However, there are two prevailing theories regarding its development. The first pertains to the disruption of the blood-brain barrier (BBB). Patients who develop ICANS have high levels of pro-inflammatory cytokines known to interact with endothelial cells of the BBB, which protects the brain from circulating toxins and pathogens.[26-28] Increased cytokine levels may lead to BBB permeabilization, allowing cytokines to enter the brain.[27] The second theory is related to the expression of CD19 on brain cells. In a study by Parker et al., a population of healthy cells in the brain were found to express CD19.[29] Since these cells express the same target antigen as the cancerous cells, CAR T-cells may mistakenly target or damage them.[29]

CAR T-cell designs and dosages may also influence the risk of developing ICANS. CAR T-cells with a CD28 cytoplasmic domain have greater proliferation, but lead to a greater incidence of ICANS.[15,31] Additionally, higher doses of CAR T-cells have been associated with an increased risk of neurotoxicity.[27,30] Further research on ICANS may help identify high-risk patients preemptively to allow for appropriate adjustments in CAR T-cell design and dosage.[31]

Treatment Logistics

Financial costs, storage, handling, and timeline of treatment all hinder the widespread clinical administration of CAR T-cell therapy. There is a concern regarding the financial burden that the treatment imposes on patients.[15] For patients with ALL, an infusion of Kymriah is over $200,000 USD more expensive than the average 100-day hematopoietic stem cell transplantation treatment (HSCT).[32,33] Nonetheless, it is important to recognize that, unlike Kymriah treatments, autologous HSCT is not curative for ALL. In a 2014 trial conducted by Maude et al., 63% (n = 30) of patients treated with Kymriah remained in remission during a follow-up period of 24 months.[34] As a result of this cost barrier, this treatment is not financially accessible to the general population. This furthers an ongoing economic debate regarding the cost-effectiveness of CAR T-cell therapies, especially due to its novelty compared to conventional cancer treatments.[32]

Moreover, the production of CAR T-cells is resource intensive, requiring genetic manipulation, quality control, and final cryopreservation of the expanded T-cell product prior to infusion.[15] Additional equipment, training, and infrastructure are also needed for the administration and post-treatment monitoring of patients. Future efforts should address the implementation in impoverished communities and hospital systems with minimal funding.

CAR T-Cell Relapse

There are two types of relapses that occur with CAR T-cell therapy. Negative CAR T-cell relapse occurs due to the loss of the target antigen on the tumor (e.g. CD19), allowing cancer cells to evade CAR T-cells.[35] Positive CAR T-cell relapse occurs due to poor persistence and proliferation of CAR T-cells despite the tumor expressing the target antigen.[5] With further use of CAR T-cells, relapse has become an apparent obstacle, with up to 50% of patients relapsing within one year.[36]

In a clinical study, CD19 CAR T-cells were administered to patients with R/R ALL, with 45% of those who achieved complete remission relapsing.[37] While positive relapse accounted for 6% of cases, negative relapse was 39%, making it a primary research focus.[37] In the case of ALL, potential treatment options include targeting the expression of CD22 on the cancer cells rather than CD19, and developing CAR T-cells with receptors able to target both CD19 and CD22.

CONCLUSION

At this stage, CAR T-cell therapy can be considered effective for inducing complete remission in hematopoietic cancer patients. Given that CRS and ICANS are heightened in patients with higher disease burden and associated comorbidities, CAR T-cell therapy administration should consider the patient's own treatment needs. Additional research is needed to better understand the mechanisms and management of multiple off-tumor toxicities. Reducing their incidence may be accomplished through alterations to individual CAR T-cell designs. Furthermore, there are a number of handling and economic challenges associated with CAR T-cell therapies. These therapies offer a promising future for those afflicted with R/R ALL and lymphomas, but its cost and patient safety concerns restrict its implementation in clinical settings.

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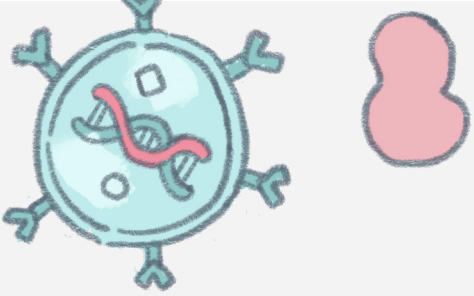

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