

CAR-T Application in hematological malignancy

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ABSTRACT

This investigation delves into the multifaceted hurdles inherent in utilizing CAR-T cell therapy to combat hematologic malignancies. It highlights the formidable financial barriers, potential adverse effects, and the quest for sustained therapeutic success. We propose an array of solutions aimed at easing the fiscal strain, refining risk identification, and amplifying therapeutic outcomes. Our strategic approaches encompass the augmentation of CAR-T cell design, the formulation of rigorous risk assessment techniques, and the advancement of sophisticated treatment management protocols. Despite the considerable impediments associated with CAR-T cell therapy, its immense prospective benefit in the realm of hematological malignancy treatment is indisputable. The convergence of technological progress and cross-disciplinary synergy heralds a new era of innovation, holding the promise of optimizing CAR-T cell design and therapeutic avenues, ultimately aspiring to yield safer, more efficacious, and enduring treatment modalities for afflicted individuals.

KEYWORDS

CAR-T; CRS; SCR; Acute lymphoblastic leukemia type B (B-ALL)

1. INTRODUCTION

The vanguard of molecular biology and immunology has catalyzed transformative advances in cellular therapy, epitomized by the groundbreaking strides in treating hematological cancers. Chimeric antigen receptor T cell (CAR-T cell) therapy has surfaced as a groundbreaking influence in this field. This study aims to scrupulously evaluate the application of this pioneering technology in the context of hematological malignancies, contemplating its potential impact, inherent challenges, and anticipated advancements. Central to CAR-T cell immunotherapy is its personalized approach, which utilizes a patient's autologous T cells, reengineered with synthetic receptor constructs, to selectively target and eliminate cancer cells. This sophisticated treatment process involves several critical stages, beginning with the separation of T lymphocytes from the individual, their subsequent genetic modification through transduction to express the CAR, their expansion in vitro to generate sufficient quantities, and finally their reinfusion into the patient following rigorous quality control measures. The intricate steps of this procedure are succinctly depicted in Figure 1 [1]. The action diagram of CAR-T.

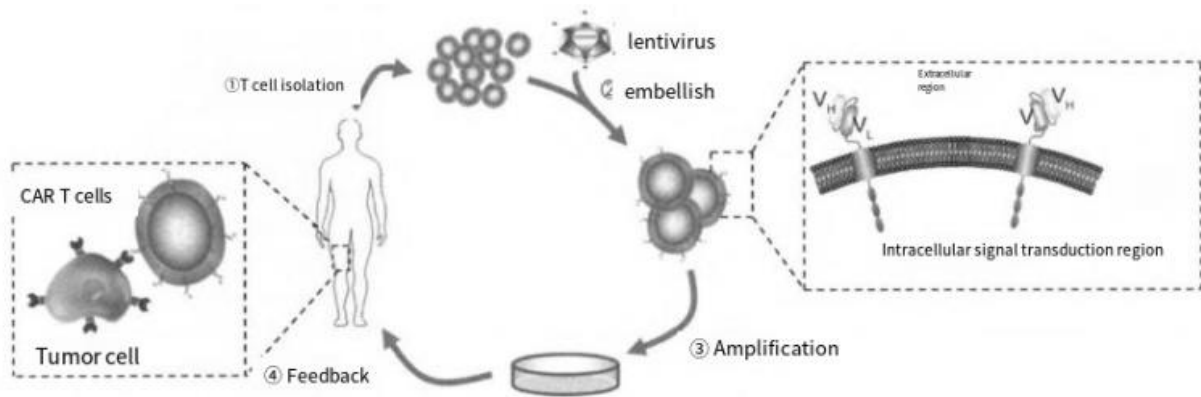


Figure 1. The action diagram of CAR-T

CAR-T cell treatment ushers in a new chapter in treatments for novel hematologic malignancies, characterized by substantial remission rates, as demonstrated by over eighty percent of patients reaching full remission in select clinical trials, particularly among those in cases of recurrent or resistant B-cell acute lymphoblastic leukemia. Moreover, as of 2023, several CAR-T cell treatment modalities have garnered validation from the United States Food and Drug Administration, stamping their efficacy for specified types of hematologic cancers and highlighting their potential for long-term disease control that extends well beyond a five-year horizon.

2. PURPOSE AND PROBLEM

2.1. Purpose

Analyze the effect of CAR-T cell immunotherapy for the management of blood cancers; explore the efficacy and its limitations; discuss existing problems and potential solution strategies; Predicts the future development direction of the technology. Principle of CAR-T cell immunotherapy and its development Design and classification of CAR-T cells. Based on the structural characteristics, the cells are divided into different generations, and the design of each generation varies in the activation power, survival time and anti-tumor ability. Current status of clinical application. The results of recent clinical experiments have shown that CAR-T cell therapy has achieved remarkable outcomes in managing specific forms of hematological cancers, including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and non-Hodgkin lymphoma (NHL).

2.2. Efficacy Analysis

Examples of the results and limitations of CAR-T in the treatment of blood cancer are as follows.

2.2.1. Acute lymphoblastic leukemia type B (B-ALL)

CAR-T The advent of cell therapy has altered the therapeutic approach for relapsed refractory (R / R) B-ALL, increasing the complete response (CR) rate of adult R / R ALL from 29% (18% to 44%) of conventional therapies to more than 80% [2-4]. The latest multicentre data on tis-cel shows, the overall CR rate for treating ALL was 81%, median survival was not attained by the time of reporting, and CAR-T persisted in the patient for more than 20 months[3]. CAR-T-19, containing another costimulatory molecule, CD28, treated 53 R / RALL with a CR rate of 83% and an overall median survival (OS) of 12.9 months.

(1) B cell deficiency represents the most frequent side effect after CAR-T-19 treatment, and the clinical application of immunoglobulin supplementation can reduce the adverse consequences due to the loss of humoral immunity. B cell deficiency can be recovered after the disappearance of CAR-T-19 in vivo.

(2) Cytokine release syndrome (CRS) represents another frequently encountered and anticipated negative outcome following treatment with CAR T-19 cells. The incidence ranges from 29% to 77%, with the severity being associated with the extent of tumor load [5,6]. This phenomenon is rare in individuals who do not show a clinical reaction to CAR treatment. The emergence of CRS has been linked to the pharmacokinetic profile of the CAR T cells, with the timing of its appearance being related to the duration of maximum proliferation of the CAR T cells within the body. In extreme instances, CRS may progress into a critical condition characterized by vascular permeability syndrome, which can lead to low blood oxygen levels and reduced blood pressure, exhibiting numerous characteristics in common with hemophagocytic lymphohistiocytosis and macrophage activation syndrome [7]. Tocilizumab (commercially known as Actemra), also referred to as Tutuzumab, is commonly an efficacious intervention for the severe CRS precipitated by CAR T-cell therapy.

(3) Beyond CRS, neurotoxic effects ranging from mild to severe have been observed, with their incidence not being directly linked to the infiltration of leukemic cells into the central nervous system [8]. Neurological side effects are seen in approximately 40% (ranging from 15% to 60%) of patients undergoing CAR T-19 therapy for ALL. These can vary from slight confusion, tremors, and challenges with speech to severe symptoms like total loss of speech, seizures, coma, and cerebral swelling. It remains unclear if the cerebral edema resulting from neurotoxicity represents a severe form of CRS or a distinct adverse consequence separate from CRS. However, the neurotoxicity ensuing from CAR T-19 administration is generally transient.

2.2.2. B-cell type non-Hodgkin lymphoma (B-NHL)

Drawing on the outcomes of three phase I clinical trials conducted at the University of Pennsylvania, the National Institutes of Health's Cancer Division, and the Sloan Kettering Institute for Cancer Research, approximately 40% of individuals suffering from B-cell non-Hodgkin lymphoma (B-NHL) attain sustained complete remission (CR) following treatment with CAR T-19 [9-11]. Despite the modest CR rates, the durability is notable: over 80% of patients who reached CR sustained it for more than a year, and fifty percent of the individuals who initially had a partial response (PR) progressed to CR within a year. Beyond the CD19-targeted CAR T therapy, CAR T cell treatments directed at CD22 have also demonstrated comparable CR rates in B-NHL.

The significant efficacy of (1)CAR-T-19 or CAR-T-20 was accompanied by the development of CRS and neurotoxicity. Different clinical trials showed the incidence of CRS from 39% to 77%, CRS over grade 3 from 1% to 23%; neurotoxicity from 15% to 68%, and that of grade 3 from 1% to 18%.

The CAR-T treatment of (2) B-NHL also includes other special adverse effects, including capillary leakage syndrome, impaired respiratory function, gastrointestinal bleeding, oncolytic syndrome and other [11-13].

2.2.3. Bozzolo's disease

The deployment of chimeric antigen receptor T-cell therapy for managing refractory multiple myeloma (MM) represents an additional area of exploration within cell-based treatment. The CAR T-BCMA therapy, which includes the 4-1BB costimulatory domain and reported by the University of Pennsylvania in the United States, exhibited the highest clinical response in patients receiving a combination of a high cell dose and cyclophosphamide (Cy), revealing a response rate of 64%. The instances of grade 3 cytokine release syndrome (CRS) and neurological toxicity were 32% and 12%, respectively [14]. Two other prominent CAR T-BCMA therapies are Bluebird Bio's bb2121 and LCAR-B38M. The phase I trial data for bb2121 indicated an elevated clinical efficacy rate of 85%, with a CR rate of 45% and a median progression-free survival (PFS) of 11.8 months. At the same time, bb2121 has a relatively low adverse efficacy percentage, along with the occurrence rates of cytokine release syndrome (CRS) and neurological toxic effects was only 3% and 6% [15]. LCAR-B38M is CAR-T cells with BCMA double epitope containing 41BB costimulatory molecules. The latest

clinical trial results in 2019 demonstrated that the overall efficacy rate of 17 refractory MM patients was 88.2%, the strict complete response rate (sCR) was 76%, and the occurrence of grade 3 or above CRS was 35% [16]. Dual-target CAR-T-cell combinations may be another promising therapeutic option for relapsed or refractory MM. Given the rapid advance in clinical trials of CAR-T cell therapy for MM, BC-MA should be the target of the second CAR-T cell product approved for market application after CD19.

Limitations: CRS and neurotoxicity

2.2.4. Chronic lymphocytic leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is a widespread B-cell malignancy of a chronic nature, predominantly impacting older adults. Despite a relatively high five-year longevity rate of 79.2%, CLL remains an intractable condition for many, especially for those with treatment-resistant or recurrent forms of the disease, who experience a particularly dire outlook [17]. The efficacy of CAR T-19 cells, similar to those employed in the treatment of acute lymphoblastic leukemia (ALL), has proven to be less impressive in managing CLL. The rates of clinical response are in the range of 50% to 70%, yet the rates of complete remission (CR) are considerably lower, ranging from just 20% to 30%. These figures starkly contrast with the more favorable outcomes associated with similar CAR T-19 therapies for ALL and B-cell non-Hodgkin lymphoma (B-NHL) [18].

(1) In the context of cytokine release syndrome (CRS), the occurrence rates spanned 50% to 100% for greater than grade 3 intensity, whereas CRS overall ranged from 25% to 60%. Neurotoxicity was comparatively rare, recorded at 0 to 35%, with instances of neurotoxicity exceeding grade 3 being notably infrequent.

(2) Recent research intimates that CAR-T cell treatment's subdued efficacy in CLL primarily stems from the patients' inherent immune challenges, which are characterized by an escalation of T cell surface markers indicative of cellular exhaustion (notably PD-1, CD244, and CD160), a scarcity of memory T cells, and reduced proliferative and cytotoxic capabilities in CD8+ T cells [19, 20].

By conducting a thorough examination of the existing clinical data, this research thoroughly characterizes the therapeutic effectiveness of CAR T cell treatment in treating different blood cell malignancies, ascertained by indicators like rates of complete remission and overall patient survival.

3. CHALLENGES AND CURRENT CONCERNS

Financial Strain from Treatment Expenses. The prohibitive cost of CAR-T cell treatment incurs a substantial economic weight for patients, while the disparate allocation of healthcare resources further constrains the treatment's accessibility. **Adverse reactions and risk management.** Throughout the course of therapy, patients are susceptible to the possibility of serious adverse effects, particularly cytokine release syndrome (CRS) and neurotoxicity. The necessity to rapidly recognize early indications of these reactions and to intervene timely is paramount. **Antigen Escape and Sustained Efficacy:** Tumor cells may circumvent CAR-T cell cytotoxicity by altering their antigen profile, thus undermining therapeutic efficacy. Furthermore, research is intensely focused on strategies to preserve the potency of these treatments over time.

4. EXPLORATION AND INNOVATION

Enhancing CAR-T Cell Design: Innovations in CAR-T cell design— through augmentation of costimulatory domains or the creation of multitarget CAR-T cells—are pivotal for bolstering in vivo functionality and durability. **Strategizing Combination Therapies:** Integrating chemotherapy, precision-targeted pharmacotherapy, and immune checkpoint blockade offers a substantial promise in amplifying the antitumor prowess of CAR-T cells. **Enhanced Treatment Management and**

Meticulous Risk Assessment: Employing a more granulated risk assessment model coupled with refined treatment management protocols is integral in mitigating the frequency of adverse events.

5. CONCLUSION

Although CAR T cell immunotherapy represents a significant advancement in the treatment of blood cancers, considerable challenges like steep expenses, the potential for adverse effects, and the endeavor to maintain treatment efficacy require dedicated resolutions in this swiftly progressing domain. Propelled by innovative developments and cross-disciplinary collaborations, the medical community is on the cusp of enhancing the framework and treatment strategies for CAR T cells, making them safer, more effective, and long-lasting, thereby widening their availability to a broader range of patients. With a deeper understanding of the tumor microenvironment and immune escape mechanisms, as well as the development of personalized treatment strategies, CAR-T cell immunotherapy is expected to become an important pillar in addressing blood cancer disorders.

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