

CAR-T Cell Therapy in Acute Lymphoblastic Leukemia

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Abstract:

Acute Lymphoblastic Leukemia (ALL) is a common blood malignancy tumor that originates from the uncontrolled growth of immature lymphocytes. This process destabilizes normal hematopoiesis and gradually deteriorates the health of patients. There are some conventional treatments such as chemotherapy and hematopoietic stem cell transplantation can improve survival for some patients. However, regarding Relapsed or Refractory (R/R) cases, their efficacy remains very limited, which is a significant challenge in clinical practice. To address these challenges, Chimeric Antigen Receptor T-cell (CAR-T) therapy has unveiled an innovative immunotherapeutic therapy. By carrying out genetic engineering on autologous T cells of patients, this strategy allows them to accurately identify and eradicate malignant lymphoblasts. Among these strategies, CD19-directed CAR-T therapy has accomplished notable clinical breakthroughs. Research shows that 70% to 90% of patients suffering from R/R ALL achieve total remission after receiving CAR-T therapy. In most cases, minimal residual disease becomes undetectable within a relatively short period. These findings also reflect this therapy can induce rapid remission and offer patients improved long-term survival outlook. At the same time, research in this field is expanding. But, in relation to safety hurdles including Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), the risk of relapse in certain patients, and the logistical challenges posed by complex manufacturing and high costs. This research explores recent research on CAR-T therapy in ALL, highlighting both its treatment developments and existing limitations. The purpose is to provide a thorough understanding that may advise future clinical practice and translational research.

Keywords: ALL; CAR-T cell therapy; Clinical outcomes.

1. Introduction

Acute Lymphoblastic Leukemia (ALL) is a type of malignant tumor that mainly caused by the unregulated proliferation of immature lymphocyte. And lead to dysfunction of hematopoiesis in the context of the bone marrow. It is among the greatest frequently encountered hematologic malignancies in young people, with an incidence of nearly 75% in this group [1]. Although traditional therapy such as Chemotherapy and hematopoietic stem cell transplantation (HSCT) has significantly enhanced survival rates over the decades. However, there are some patients who still experience relapse or refractory disease, with a five-year survival rate of only 10-20% [2].

In recent years, the occurrence of immunotherapy provides new hope for ALL treatment. Fortunately, CAR stand out prominently. This is an engineered receptor comprise single-chain variable fragment (SCFV), transmembrane domain and intracellular signaling domain. It enables T cells to detect and kill tumor cells independently of the major histocompatibility complex (MHC) [3].

When the T cells of the patient are genetically modified to express a CAR, that is called CAR-T cells. These cells are expanded outside the body and then reintroduced into patients where they selectively target malignant cells. Most clinical trials involving individuals with R/R ALL have reported high remission rates following CAR-T therapy, such as CD19-targeted CAR-T which reaching over 80% [4].

This paper summarizes research advances of CAR-T cell therapy in the treatment of ALL. Focusing on its mechanism of action, clinical application, challenges and limitations, and future directions. The author seeks to furnish clinicians with a reference to help optimize treatment strategies.

2. Mechanism of CAR T-Cell Therapy

The CAR usually consists of three parts. First and foremost, the extracellular antigen-recognition domain is mostly sourced from scFv, which is used to specifically bind tumor-associated antigens such as CD19. This region defines the specificity of CAR-T cell targeting and enables them to discriminate between malignant cells and normal cells. Then, the transmembrane domain plays a key role in linking the extracellular and intracellular signaling regions, which stabilizing the overall receptor structure. Last but not least, the intracellular signaling domain transmits critical activation signals. It consists of two parts, the CD3 zeta chain (CD3 ζ) signaling unit, derived from the native T-cell receptor complex, and one or more co-stimulatory molecules such as CD28 or cluster of Differentiation 137

(4-1BB). The former triggers T-cell activation, while the latter enhances their proliferative capacity and persistence in vivo [3].

When CAR-T cells interact with antigens located on tumor cells. This binding triggers intracellular signaling, which in turn activates T cells. Activated CAR-T cells eliminate tumor cells through the release of granzymes and perforin, which induce apoptosis. They also secrete cytokines such as Interferon-gamma (IFN- γ) and Tumor Necrosis Factor-alpha (TNF- α) to strengthen anti-tumor immunity [5]. CAR-T cells not only directly kill target cells but furthermore modulate the tumor microenvironment to relieve immunosuppression and enhance therapeutic efficacy.

Moreover, CD19-targeted CAR-T cells are the most advanced in ALL research and clinical practice. This is because CD19 is highly expressed on most B-cell leukemia and lymphoma cells, while its expression on hematopoietic stem cells and other tissues are limited. And the clinical studies have shown that this therapy achieves complete remission (CR) proportions above 80% in patients with R/R ALL [4]. Researchers are also dedicated to optimizing the design of CAR-T cells and enhancing their persistence. Additionally, they are exploring dual-target or combination therapies to reduce relapse rates and improve overall therapeutic efficacy.

3. Clinical Applications in ALL

The clinical application of CAR-T cell therapy has made significant progress in R/R B-cell ALL. Many studies have shown that individuals undergoing CD19 CAR-T cell treatment can achieve CR rates of 70-90%, with most reaching MRD-negative status within a short time [6,7]. For example, a study of Tisagenlecleucel for children and teenager R/R ALL patients reported an 81% CR rate after three months, with over 60% of patients reaching MRD-negative status [6]. These research results highlight that CAR-T therapy works quickly and powerfully to induce remission, which is especially important for patients who have limited choices after trying conventional treatments.

Notably, adult patients also experience significant therapeutic benefits. In a multicenter study of adult R/R ALL patients, CD19 CAR-T therapy achieved a 76% CR rate. With a median follow-up of 12-months, the event-free survival (EFS) and overall survival (OS) were approximately 50% and 60% [7]. In order to assess efficacy and safety more objectively, these studies are mostly prospectively designed or some incorporating historical controls.

Clinically, CAR-T cells are usually infused after lympho-depleting chemotherapy to enhance their expansion and

persistence. This preconditioning reduces competition from endogenous lymphocytes and optimizes the *in vivo* environment, thereby enhancing the anti-tumor activity of these cells [8]. While, the efficacy is usually measured by MRD negativity, CR, EFS, and OS. Multi-center studies and standard evaluation methods make the results more comparable.

In the future, studies can improve reliability by increasing sample sizes and extending follow-up periods and optimizing efficacy measures. Different CAR designs, such as those CD28 or 4-1BB costimulatory domains who may lead to variations in therapeutic outcomes and toxicity profiles. Moreover, the combination of CAR-T cells with targeted medications or antibodies could further improve clinical benefit and provide guidance for their wider application.

Additionally, integrating CAR-T therapy with targeted drugs, monoclonal antibodies, or other supportive treatments not only enhances its anti-tumor effects but also makes it appropriate for more types of patients. Although remaining challenges such as safety issues still exist, careful patient monitoring and standardized protocols for treatment can effectively reduce these problems. Carrying out multi-center collaborations and consistent evaluation methods will be vital to collect reliable data. They will also help support clinical decisions and promote the wider utilization of this therapy in standard clinical practice.

4. Challenges Facing CAR-T Therapy in ALL

This therapy has shown significant efficacy in ALL. However, its clinical still linked to certain adverse effects. The main adverse reactions are CRS and ICANS. These conditions can differ in how severe they are and can be anything from mild clinical symptoms to severe and complications that could be life-compromising. They are caused by the powerful immune system activation set off by CAR-T cells, which can cause inflammation throughout the body and impact several organ systems. Along with CRS and ICANS, some patients may experience other side effects such as prolonged cytopenia, higher chance of getting infections, or temporary problems with organ function. Understanding the causes of these negative reactions and figuring out who might be at risk are essential steps to boost the safety profile and practicality of this therapy when used in hospitals.

4.1 CRS

This is a common and potentially severe adverse effect of this therapy. It caused by rapid activation and the large

release of cytokines for example, IL-6, IFN- γ and TNF- α . Its symptom is fever, hypotension and hypoxemia, even progress to multi-organ dysfunction in severe cases [9]. From a clinical perspective, it occurs in about 77% of children and teenagers with R/R ALL, approximately 46% of whom are grade 3-4 and need intensive [6]. Today, Tocilizumab (TCZ) has become the main treatment for CRS and can rapidly alleviate symptoms in many cases [9].

4.2 ICANS

That is another common adverse effect, which usually occurs after or concurrently with CRS. Nowadays, its mechanism has not been fully understood, but it might be associated with an increase in permeability of the blood-brain barrier and the entry of inflammatory cytokines into the central nervous system. Clinically, it manifests altered consciousness, seizures, language disturbances, and elevated intracranial pressure [10]. For ALL patients administered CD19 CAR-T therapy, ICANS occurs in approximately 40% of cases, with 10–15% classified as grade 3 or higher [6]. And, glucocorticoids are the primary clinical intervention for ICANS, though TCZ demonstrates limited efficacy.

4.3 Other Adverse Effects

Besides the CRS and ICANS, CAR-T therapy may cause prolonged B-cell aplasia, leading to hypogammaglobulinemia and an increased risk of infections [9]. These long-term complications show that post-CAR-T follow-up monitoring and immunoglobulin replacement therapy are necessary. Also, some patients could have cytopenia, fatigue, or other mild damage to organs following CAR-T cell infusion. These side effects are usually easy to handle in most patients. They even highlight how important it is to thorough care after treatment and personalized care plans to keep patients safe and help them have better overall results.

5. Limitations Associated with CAR-T Therapy for ALL

There are some patients may still experience after treatment. The main reason for is attributed to antigen escape, for instance, loss of CD19 expression, and insufficient *in vivo* persistence of CAR-T cells. Clinical data indicate roughly 30-50% of patients relapse within 6-12 months following treatment [4].

Another major challenge is the extended production timeline and high cost of CAR-T, which adding therapeutic challenges and economic burden. Autologous CAR-T therapy requires collection of T cells from the patients,

followed by genetic modification and expansion in vitro, and then reinfusion. The whole process usually takes 2 to 4 weeks. Therefore, the substantial manufacturing and treatment expense restrict the availability of this therapy in regions with scarce resources. Although off-shelf allogeneic CAR-T cells are regarded as a potential resolution, their safety remains uncertain. Moreover, the hazards of graft-versus-host disease (GVHD) immune rejection and immune rejection still require advanced evaluation.

Ultimately, individual patient differences and the heterogeneous nature of tumors can affect treatment outcomes. The availability of adequate healthy T cells is not universal, with elderly or immunodeficient patients may even be unable to undergo CAR-T therapy. Moreover, differences in the tumor microenvironment across patients can further affect treatment quality.

To sum up, adverse effect, relapse risk, interindividual variability and manufacturing challenges remain the major barriers to the expanded application of this therapy in the clinical management of ALL. To make this therapy a truly accessible treatment option, future research should focus on reducing toxicity, extending efficacy and improving manufacturing processes.

6. Future Perspectives

Given the persistent challenges of relapse risk, durability of response, and safety in CAR-T therapy currently used for R/R ALL, future research is primarily focused on several key directions.

Multi-antigen CAR-T strategies represent one focus of current research combined with safety switch designs. Single-target therapies are prone to antigen escape, which increases the risk of relapse. To overcome this, researchers are developing dual-target CAR-T cells targeting both CD19 and CD22 [11]. At the same time, safety switch designs can be implemented to rapidly eradicate CAR-T cells when the adverse events happening, thereby increasing treatment safety.

In contrast, prolonging the in vivo persistence of this cell is also an important goal. One cause of relapse in some patients is the limited survival period of this cell within the body. To prolong the in vivo persistence of CAR-T cells and improve long-term efficacy, researchers have optimized the co-stimulatory domains, such as CD28 or 4-1BB, and selected memory T cell subsets [12].

Moreover, the advancement of universal or allogeneic CAR-T cells provides a new opportunity to increase the accessibility of this therapy. Unlike autologous CAR-T cells, allogeneic CAR-T cells furnish an off-the-shelf solution, which shortens production cycles and lowers treatment costs. As a result, more patients in areas with

limited resources can gain access to CAR-T treatment [13].

7. Conclusion

To address R/R ALL, CAR-T cell therapy has made significant advances never seen before. It provides an alternative for patients who show limited response to conventional treatments. By aimed at abnormal lymphoblasts, CAR-T helps researchers control conditions that were previously difficult to control and also offers new ideas for formulating treatment strategies. However, even with these advancements, safety is still a critical challenge, which has restricted its widespread use in the clinical setting. Some side effects, such as CRS and ICANS, as well as possible long-term toxic effects. It requires doctors to keep patients under close observation and react quickly if problems arise, and customize treatment plans for each condition of patients. Besides that, CAR-T therapy faces several inevitable challenges. The manufacturing process is extremely complex, requiring advanced equipment and facilities, and the costs remain very high. Together, these factors limit the broad implementation of the therapy, so not all patients can receive treatment. To overcome these challenges in the future, research could focus on several directions. First, improving the design of CAR-T cells and the pre-treatment protocols. Second, developing ready-to-use allogeneic products. Then, exploring dual-target or multi-target CAR-T cells. Studying how CAR-T therapy is used together with other treatment approaches could achieve better results continuous gathering and assessment of long-term safety data will also be essential for understanding delayed toxicities and improving patient management. Overall, this therapeutic approach shows potential for treating leukemia. However, to make it readily available to more patients, several issues need to be addressed. Its safety must be improved and risks controlled, and the therapy must be made available and affordable. Only by addressing these challenges can CAR-T become a feasible and effective option in clinical practice.

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