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Progress and Challenges in the Application of CAR T-Cell Therapy for Hematologic Malignancies

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Abstract. With an aging population and changes in environmental and lifestyle factors, the incidence of hematologic malignancies has been increasing worldwide. Diseases such as leukemia, lymphoma, and multiple myeloma are often characterized by rapid progression and high relapse rates, posing a serious threat to human health. Conventional treatment modalities, including chemotherapy, radiotherapy, and transplantation of hematopoietic stem cells, have demonstrated limited efficacy among individuals with relapsed or refractory hematologic malignancies. Drug resistance, low remission rates, and poor prognosis remain major clinical concerns, underscoring the pressing demand for innovative therapeutic approaches capable of addressing the limitations of current treatments. Chimeric antigen receptor T-cell (CAR T-cell) therapy is widely regarded as a significant advancement in the field of cancer immunotherapy. Owing to its precise targeting and potent antitumor activity, CAR T-cell therapy has provided a novel treatment option for individuals affected by relapsed or refractory hematologic malignancies. Based on relevant literature review and inductive analysis, this review offers a comprehensive overview of recent progress regarding the clinical use of CAR T-cell therapy for a range of hematologic malignancies. It focuses on the major challenges associated with clinical application, particularly cytokine release syndrome, tumor immune evasion, and high treatment costs. In addition, current technological improvements and clinical optimization strategies are discussed, and future development trends are explored. Existing evidence indicates that, compared with conventional treatment modalities, CAR T-cell therapy provides clinically meaningful benefits for individuals with relapsed or refractory hematologic malignancies. It can improve remission rates and clinical outcomes and therefore has considerable clinical value. However, several limitations remain, including the risk of serious adverse events, tumor immune evasion, and high costs, all of which substantially hinder its clinical translation and widespread application.

Keywords: CAR T-cell therapy, hematologic malignancies, immunotherapy, cell therapy, leukemia

1. Introduction

The rapid development of genetic engineering and tumor immunology has facilitated the emergence of chimeric antigen receptor T-cell (CAR T-cell) therapy as an innovative strategy in cancer

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immunotherapy, providing a new treatment option for patients with relapsed or refractory hematologic malignancies. First-generation CARs were composed solely of one CD3ζ signaling domain and did not include costimulatory signals, which led to insufficient antitumor activity and ultimately prevented their continued use in clinical practice. By incorporating costimulatory domains, including CD28 and 4-1BB, second-generation CARs markedly improved T-cell activation and persistence, making them the predominant CAR platform in current clinical practice. Although third-generation CARs contain two costimulatory domains, they have not demonstrated clearly superior clinical benefits, while concerns regarding their safety have largely limited their application to clinical trials. The design of fourth-generation "armored" CARs enables them to release cytokines while modifying the tumor immune microenvironment. Fifth-generation CARs employ CRISPR-Cas9-based gene-editing technologies to support multiplex genetic modifications, with the goal of advancing CAR T-cell therapy toward broader applicability, greater safety, and longer-lasting therapeutic effects.

Despite the well-established therapeutic value of CAR T-cell therapy in hematologic malignancies, several limitations remain in the existing body of research. A considerable proportion of previous reviews have examined only one specific dimension, including therapeutic efficacy, complications, or technological development, without providing an integrated analysis of CAR structure and mechanisms, its complete evolutionary history, clinical challenges, and corresponding optimization strategies. As a result, the existing research has not yet formed a coherent and comprehensive framework [1].

In light of these considerations, the present review examines the development and clinical progress of CAR T-cell therapy in hematologic malignancies. By reviewing the literature and applying an inductive approach, this study synthesizes high-quality international and domestic publications together with clinical trial data, with the aim of outlining the fundamental principles of CAR T-cell therapy, the defining features of its five generations, and its clinical effectiveness. The review places particular emphasis on key obstacles to clinical application, such as cytokine release syndrome, tumor immune escape, and the substantial costs associated with treatment. In addition, the review evaluates existing approaches for improvement and considers the potential directions of future development.

2. Clinical progress of CAR T-cell therapy in hematologic malignancies

Hematologic malignancies generally exhibit relatively distinct antigen expression patterns, widespread tumor-cell distribution in the blood and lymphoid organs, and favorable accessibility of CAR T cells to the tumor sites. For these reasons, hematologic malignancies are regarded as the disease category most amenable to CAR T-cell therapy and have demonstrated particularly notable clinical benefits. Significant clinical advances have been reported across three principal disease groups, namely acute leukemia, lymphoma, and multiple myeloma.

2.1. Acute leukemia

Acute leukemia comprises two primary subtypes: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). CAR T-cell therapy has demonstrated promising therapeutic potential against both malignancies.

For patients with B-cell acute lymphoblastic leukemia (B-ALL), CAR T-cell therapy has yielded some of the most encouraging clinical outcomes reported to date. In pediatric and young adult patients with relapsed or refractory B-ALL, CD19-targeted CAR T-cell therapy is linked to high

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complete remission rates, and a subset of patients can also attain minimal residual disease (MRD) negativity. These findings provide an alternative therapeutic option for patients with insufficient responses to prior therapies [2]. Data from multiple clinical trials demonstrate that CD19 CAR T-cell therapy can substantially reduce tumor burden and may enable eligible patients to receive subsequent hematopoietic stem cell transplantation.

Because CD19 is not typically a dominant tumor-associated antigen in AML, conventional CD19 CAR T-cell therapy has limited applicability, and the selection of appropriate target antigens has become a major concern. Current clinical investigations are evaluating several potential targets, including CD123, CD33, CD38, CD117, and CLL-1. In a proportion of patients, these antigens can be detected on AML cells or leukemia stem cells. Early investigations have reported preliminary antileukemic activity from CAR T cells directed against these antigens. Nevertheless, their further development remains hindered by several limitations, including damage to normal hematopoietic cells, inadequate target specificity, and the short duration of therapeutic responses.

Notably, CD19/CD22 dual-target CAR T-cell therapy has shown promise as an approach to managing relapse associated with CD19 antigen loss or downregulation in B-ALL. Findings from initial clinical studies suggest that dual-target CAR T cells retain antitumor activity and may help lower the risk of antigen escape observed with single-target therapy .

2.2. Malignant lymphomas

Malignant lymphomas can be broadly divided into Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). Among NHL cases, B-cell NHL constitutes a substantial proportion and is regarded as an important clinical indication for CAR T-cell therapy.

For patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), CD19 CAR T-cell therapy has emerged as a clinically important therapeutic option. Evidence from clinical studies indicates that CD19 CAR T-cell products, including axicabtagene ciloleucel, can achieve relatively high objective response rates and complete remission rates among patients with refractory large B-cell lymphoma. A proportion of treated patients may experience sustained responses accompanied by prolonged survival [3]. In comparison with conventional salvage chemotherapy, CAR T-cell therapy offers an alternative therapeutic strategy for patients whose disease has progressed after multiple lines of treatment.

Favorable therapeutic responses to CAR T-cell therapy have also been observed in both indolent and aggressive lymphomas, such as follicular lymphoma and marginal zone lymphoma. In patients with high-risk disease, relapse, multiple relapses, or transplant ineligibility, CAR T-cell therapy may function as an important salvage approach by rapidly decreasing tumor burden and enhancing disease control. Results from the ZUMA-5 study showed that axicabtagene ciloleucel produced relatively high response rates and complete remission rates in patients with relapsed or refractory indolent NHL, thereby providing clinical support for the use of CAR T-cell therapy in indolent lymphomas [4].

2.3. Multiple myeloma

Multiple myeloma (MM) represents a malignant plasma-cell clonal disorder characterized by a relapsing clinical course and remains generally incurable. Standard therapeutic approaches comprise proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, as well as hematopoietic stem cell transplantation. Nevertheless, a subset of patients ultimately develops resistance to multiple drugs or experiences disease relapse. Because B-cell maturation antigen (BCMA) is

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selectively detected or present at relatively high levels on myeloma cells, it has become a major molecular target for CAR T-cell therapy in MM.

BCMA-targeted CAR T-cell therapy has markedly reshaped the therapeutic landscape for individuals with relapsed or refractory MM. BCMA CAR T-cell products, particularly idecabtagene vicleucel (ide-cel, Abecma), have achieved high overall response rates and substantial response depth among subjects with relapsed or refractory MM who have received multiple lines of therapy. Sustained disease control can be achieved in a proportion of patients [5].

Furthermore, emerging targets, including GPRC5D, CD37, and SLAMF7, are progressively being evaluated in clinical studies. Targeting these molecules may help address relapse associated with decreased or absent BCMA expression, while also broadening the clinical application of CAR T-cell therapy in MM.

3. Key challenges in the clinical application of CAR T-cell therapy

Although CAR T-cell therapy has shown remarkable antitumor activity against relapsed or refractory hematologic malignancies, a number of obstacles still hinder its widespread clinical use and long-term application. The principal challenges involve severe adverse events, disease relapse after treatment, substantial therapeutic costs, and a restricted range of indications [1].

3.1. Adverse events and safety risks

The clinical application of CAR T-cell therapy may also give rise to cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), either of which can result in a life-threatening condition or even prove fatal in some cases. In addition, patients may experience cytopenias, infections, hypogammaglobulinemia, and other persistent toxicities, thereby complicating subsequent clinical management.

CRS represents one of the most frequently observed immune-related adverse events after CAR T-cell therapy. The rapid in vivo activation and proliferation of CAR T cells may cause the substantial release of inflammatory cytokines over a brief period, consequently triggering a systemic inflammatory response. Its clinical features may involve high fever, hypotension, hypoxemia, capillary leakage, as well as hepatic or renal dysfunction. To facilitate the clinical recognition, classification, and treatment of these toxicities, the American Society for Transplantation and Cellular Therapy (ASTCT) has developed standardized grading criteria for CRS and ICANS [6].

ICANS may present clinically with headache, confusion, language impairment, seizures, and cerebral edema in severe cases. Although the underlying mechanism remains incompletely understood, it may be associated with systemic inflammation, disruption of the blood-brain barrier, and cytokine-mediated neurological damage. For patients who develop severe ICANS, timely neurological monitoring and standardized treatment are essential [6].

Persistent B-cell aplasia, hypogammaglobulinemia, recurrent infections, and prolonged cytopenias may also occur as long-term complications. Such complications may impair patients' long-term quality of life and necessitate continuous immunologic support together with measures to prevent infection.

3.2. Tumor relapse and immune escape

Disease relapse following CAR T-cell therapy remains one of the major obstacles to achieving durable clinical benefit. Tumor cells may acquire genetic mutations, undergo clonal selection, and be

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subject to epigenetic regulation, resulting in the downregulation or loss of target antigen expression. Commonly involved targets include CD19 and BCMA. As a result, CAR T cells may fail to efficiently recognize and eliminate tumor cells, which is referred to as tumor antigen escape [7].

Tumor cells may also impair the efficacy of CAR T-cell therapy by altering antigen processing and presentation, enhancing immunosuppressive signaling, and remodeling the tumor microenvironment. Sustained exposure to tumor antigen stimulation and an immunosuppressive microenvironment can induce CAR T-cell exhaustion. Exhausted CAR T cells frequently express high levels of inhibitory receptors, including PD-1, TIM-3, and LAG-3, leading to reduced proliferative capacity and antitumor activity [7].

In addition, factors with immunosuppressive properties within the tumor microenvironment, such as TGF-β, IL-10, and adenosine, together with immunosuppressive cell populations, including regulatory T cells and tumor-associated macrophages, may form a suppressive barrier that limits CAR T-cell activity. In some patients, insufficient in vivo persistence of CAR T cells prevents the establishment of long-term immunological memory and the complete eradication of minimal residual disease, ultimately contributing to relapse.

3.3. High manufacturing costs and limited accessibility

Most CAR T-cell products applied in current clinical practice are autologous, patient-specific therapies. They are associated with long manufacturing cycles, complex production procedures, high costs, and limited accessibility [8].

First, the manufacturing process is complex. It requires the collection of autologous T cells, followed by ex vivo genetic modification, cell expansion, quality control, and reinfusion into the patient. The entire process requires a certain amount of time, and patients with rapidly progressive disease may experience clinical deterioration while awaiting product manufacture.

Second, CAR T-cell production involves multiple stages, including viral-vector production, gene transfer, good manufacturing practice (GMP)-compliant manufacturing, quality testing, and cold-chain transportation. These requirements contribute to high production costs and make a single treatment course prohibitively expensive for many families.

Finally, differences in manufacturing capacity, the distribution of medical resources, and the extent of insurance coverage mean that some eligible patients cannot receive treatment in a timely manner. The establishment of global manufacturing capacity and standardized production systems is an important strategy for improving accessibility and reducing manufacturing costs [8].

3.4. Limitations in solid tumors and special populations

Despite the substantial success of CAR T-cell therapy in hematologic malignancies, its efficacy in solid tumors remains unsatisfactory. In addition, its safety and efficacy in older adults, patients with organ dysfunction, and those with multiple comorbidities require further investigation.

The major barriers to the treatment of solid tumors include marked tumor antigen heterogeneity and the lack of broadly expressed, highly specific target antigens. In addition, dense tumor architecture and extensive fibrosis can impede CAR T-cell penetration. A highly immunosuppressive local tumor microenvironment may induce CAR T-cell exhaustion, while abnormal tumor vasculature can impair the trafficking and infiltration of CAR T cells.

In older patients, individuals with organ dysfunction or multiple comorbidities, and patients with a reduced number of T cells or impaired T-cell function, CAR T-cell expansion may be

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compromised, potentially affecting both efficacy and tolerability. Therefore, individualized risk assessment and optimized treatment strategies for special populations are of critical importance.

4. Improvement strategies and research trends in CAR T-cell therapy

To overcome the limitations of CAR T-cell therapy, including inadequate safety, relatively high relapse rates, high treatment costs, and restricted applicability, current research primarily focuses on structural optimization, gene editing, safety management, cost reduction, combination therapy, and the development of novel targets.

Structural modification and gene editing represent important strategies for boosting the function of CAR T cells. Modifications to the single-chain variable fragment, hinge region, transmembrane domain, and costimulatory domains may improve antigen recognition, tolerance to exhaustion, and in vivo persistence. In addition, CRISPR-Cas9 and other genome-editing technologies are capable of being utilized to alter T-cell receptor genes, immune checkpoint genes, and other functionally relevant genes, thereby enhancing the anti-tumor potency of CAR T cells.

To address antigen escape, CD19/CD22 dual-target CAR T cells are engineered to identify two B-cell-associated antigens concurrently, which may reduce the probability of treatment failure resulting from the downregulation of a single antigen [9]. In addition, multitarget CAR T cells along with tandem CAR T cells and bispecific CAR T cells have emerged as promising strategies for tackling tumor heterogeneity as well as antigen escape.

During the engineering of universal CAR T-cell products, gene-editing techniques can be employed for knocking out the T-cell receptor alpha chain and additional relevant genes, thereby reducing the likelihood of graft-versus-host disease linked to allogeneic T cells. This strategy may facilitate the production of off-the-shelf, non-patient-specific CAR T-cell products. Preliminary studies have demonstrated that universal gene-edited CAR T cells are able to achieve molecular remission in certain pediatric patients with B-ALL, indicating their potential to reduce manufacturing time and enhance treatment accessibility [10].

In terms of clinical safety management, comprehensive and graded systems for the prevention and management of adverse events have gradually been established. Real-time monitoring of vital signs, inflammatory cytokine levels, and neurological status can facilitate early warning. Differentiated intervention strategies should be developed according to the severity of CRS and ICANS. In addition, controllable safety-switch systems should be further developed to achieve a better balance between therapeutic efficacy and safety.

At the industrial and cost-control levels, the development of universal CAR T-cell products, in vivo CAR T-cell generation technologies, domestic manufacturing processes, and multilayered medical insurance systems may overcome the limitations of conventional individualized manufacturing, reduce treatment costs, and improve accessibility [8].

Combination therapy and the exploration of novel targets are also important strategies for reducing relapse and overcoming drug resistance. CAR T-cell therapy may be combined with immune checkpoint inhibitors, chemotherapy, targeted agents, and hematopoietic stem cell transplantation to achieve synergistic antitumor effects. Meanwhile, the continued identification of novel targets, including GPRC5D, CD37, and SLAMF7, is expected to further broaden the clinical applicability of CAR T-cell therapy.

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5. Conclusion

CAR T-cell therapy represents a milestone achievement in cancer immunotherapy. With precise targeting, strong cytotoxic effects, and the ability to induce immunological memory, it has reshaped the therapeutic approach for some individuals with relapsed or refractory hematologic malignancies. CAR T-cell therapy has demonstrated promising clinical outcomes within acute lymphoblastic leukemia, malignant lymphoma, and multiple myeloma, thereby offering new therapeutic options for subjects who fail to respond to conventional chemotherapy, precision therapy, or transplantation [1-5].

Nevertheless, the broader clinical use of CAR T-cell therapy continues to be limited by several challenges, including severe acute toxicities such as CRS and ICANS, post-treatment relapse, tumor antigen escape, prolonged manufacturing timelines, high treatment costs, and the unequal distribution of medical resources [1, 6-8]. Its efficacy and safety in solid tumors, older patients, and other special populations also remain in need of further improvement.

Current research largely emphasizes the optimization of CAR molecular structures, the incorporation of gene-editing technologies, the standardization of adverse-event prevention and management, the industrial development of universal CAR T-cell products, the design of dual- and multitarget CAR T-cell therapies, the investigation of combination regimens, and the identification of novel antigen targets. Studies of CD19/CD22 dual-target CAR T cells and universal gene-edited CAR T cells have introduced new approaches to decreasing the risk of antigen escape, reducing manufacturing time, and enhancing treatment accessibility [9, 10].

Looking ahead, progress in universal CAR T-cell products, in vivo manufacturing technologies, and novel gene-editing approaches may gradually change CAR T-cell therapy from an expensive and individualized treatment into a standardized, accessible, and widely available therapeutic option. However, these technologies still need to be assessed in larger clinical trials and by means of long-term follow-up before their long-term efficacy, safety, and real-world clinical value can be adequately confirmed.

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