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Current status and progress of research on CAR-T Cell Therapy for the treatment of hematological malignancies

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Abstract. Chimeric antigen receptor T-cell (CAR-T) therapy, which first entered clinical use in 2010, it has achieved notable advancements in the treatment of blood cancers, leveraging the genetic modification of T cells to identify and destroy cancer cells. Some conditions like acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma can be effective treated with this therapy, this is important because of the premise that various previous therapies have failed. The aim of this therapy is to make T cells express chimeric antigen receptors, a process that requires engineering them, enabling them to specifically recognize tumor antigens, such as CD19. Despite the promising outcomes, challenges remain, this is accompanied by side effects that are more distressing to patients, such as neurotoxicity, as well as limited efficacy in solid tumors. Recent research efforts are focused on optimizing CAR design, enhancing T cell Chimeric Antigen Receptor T-cell (CAR-T) therapy represents a groundbreaking advancement in the treatment of hematologic malignancies persistence, and expanding applicability to solid tumors. Developments of bispecific and allogeneic CAR-T cells, and combination therapies are being explored to mitigate current limitations. This review discusses the mechanism of action, clinical applications, and future directions of CAR-T cell therapy, emphasizing its transformative potential and the ongoing efforts to coping with the difficulties of the moment.

Keywords: CAR-T cell therapy, Hematological malignancies, Immunotherapy.

1. Introduction

In recent years, this therapy achieves targeted killing of tumors by transforming the T-cells into cells with specific tumor antigen-recognition capabilities [1]. Since the first FDA approval of a CAR-T product for blood cancers' treat in 2017, the therapy has been widely used for addressing a broad spectrum of refractory and relapsed hematological malignancies, including lymphoma and multiple myeloma. Nevertheless, the widespread use of CAR-T therapy still faces many challenges, such as treatment-related toxicity, long-term effects of treatment, and treatment cost. Existing studies have shown that it has demonstrated high complete remission rates in the treatment of hematological malignancies, but the durability of efficacy remains unclear. Particularly in patients with multiple myeloma, despite significant initial efficacy, subsequent recurrence rates are high, suggesting the need to further optimize the design and manufacturing process of CAR-T cells [2]. In addition, treatment-associated cytokine release syndrome (CRS) and neurotoxicity (ICANS) are significant factors limiting the application of this therapies, and how to effectively predict and manage these adverse effects is the

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focus of current research. This study will pay attention on the current status of CAR-T cell therapy in hematological malignancies, specifically including evaluation of clinical effectiveness and safety of acute lymphoblastic leukemia, lymphoma and multiple myeloma.Also, this study will explore the differences in specific antigen recognition and killing effects of different CAR-T cell products and how these differences affect the efficacy and incidence of side effects.Through a systematic review of relevant literature, the study in order to to summarize the current advantages and shortcomings of this therapy, and to provide guidance for future clinical applications and research.The significance of this study is that it will not only help to deepen the comprehension of how it works and clinical application of it in hematological malignancies, but will also provide theoretical support for optimizing the existing therapies, reducing the side-effects, and improving the therapeutic efficacy. Meanwhile, this study will provide a key recommendation for future direction of new CAR-T cell products and therapeutic strategies, thus promoting the further development of this field [3].

2. Overview and Mechanism of CAR-T Cell Therapy

2.1. Overview of CAR-T-cell therapy

This treatment represents a groundbreaking method for cancer immunotherapy, mainly utilized for hematological cancers. It functions use genetically modifying the patient's T-cells, enabling them to generate chimeric antigen receptors (CARs) that can identify and eliminate targeted tumor cells. Developers of this therapy initially faced several challenges, for instance, the inhibition of therapeutic effects by the tumour microenvironment. But now CAR-T therapy has gradually overcome these challenges and has demonstrated significant efficacy [4].

2.2. Mechanism of action

The core of this therapy is genetic modification. The process begins by collecting patients' T cells and introducing the gene encoding the chimeric antigen receptor (CAR) into the T cell genome via a viral vector or non-viral vector. Chimeric antigen receptors usually consist of three functional domains: an extracellular antigen recognition region (usually a single-chain antibody fragment), a transmembrane region, and an intracellular signal transduction region. The structure of CAR-T cells and their mechanism of action are illustrated in Figure 1. CAR recognizes specific antigens on the surface of cancer cells, such as the CD19 antigen (commonly found in B-cell hematological tumours), and activates the killing function of T-cells through intracellular signal transduction regions. Activated T cells release cytokines that initiate a cytotoxic response, thereby destroying the target tumor cells [5].In addition, CAR-T cells can proliferate in vivo to form "active drugs" that continue to seek out and kill remaining tumor cells for a certain period of time.This property gives therapy a significant long-term tumor-inhibiting potential. Mechanism of action of CAR-T cells is shown as Figure.1.

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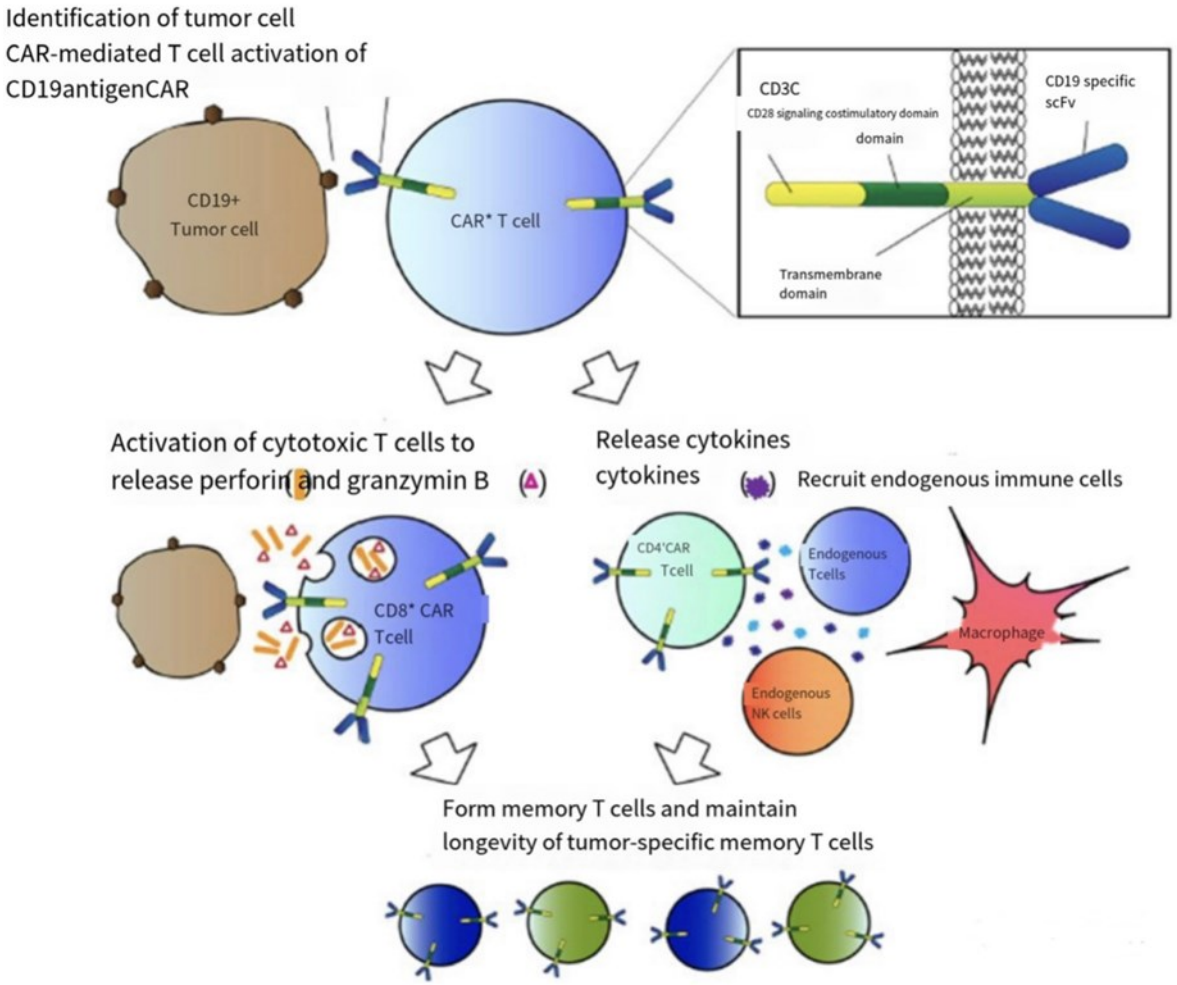

Figure 1. Mechanism of action of CAR-T cells[6]

3. Clinical Application of CAR-T Cell Therapy in Hematologic Malignancies

3.1. Leukemia

For managing Acute Lymphoblastic Leukemia, ALL in children, this therapy has achieved significant success. ALL is for which conventional treatment options are often ineffective in relapsed or refractory cases. However, CAR-T therapies offer new treatment options for these patients. Kymriah (tisagenlecleucel) was the first CAR-T cell therapy granted FDA approval, specifically for treating patients with ALL. In clinical trials, tisagenlecleucel has demonstrated impressive remission rates. According to Maude et al, 52 out of 68 patients with relapsed or refractory B-cell ALL achieved complete remission after treatment with tisagenlecleucel, and the majority of patients maintained disease-free survival for the following 12 months [7]. Despite the remarkable efficacy of this therapy in leukemia patients, there are still some challenges in the treatment process, especially the occurrence of cytokine release syndrome (CRS), a serious side effect that usually occurs in the early stages of treatment and is characterised by an overactive immune response, which may lead to multi-organ failure. In most cases, the use of tolizumab, an IL-6 receptor antagonist, is effective in alleviating the symptoms of CRS [8].

3.2. Lymphoma

It has also demonstrated significant efficacy in the treatment of B-cell lymphoma, particularly in the

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treatment of large B-cell lymphoma (DLBCL). Yescarta is the first FDA-approved CAR-T cell therapy for treating this kind of disease. In a ZUMA-1 trial, 82% of 101 patients with relapsed to Yescarta, with 54% achieving complete remission [9]. Extended monitoring data show that some patients remain in complete remission more than two years after treatment. Although this therapy has shown notable results in lymphoma patients, patients may experience relapse after treatment. This may be related to the lack of persistence of CAR-T cells in the body. In order to solve issue, experimenters are exploring ways to enhance the persistence of CAR-T cells, such as extending T-cell lifespan through gene editing or developing bispecific CAR-T cells [10].

3.3. Multiple myeloma

These therapies have demonstrated increasing medical achievement have attracted widespread attention. Multiple myeloma is a refractory hematological malignancy in which patients often show resistance to conventional therapies and have a poor prognosis. Abecma (Idecabtagene Vicleucel) is the first FDA-approved BCMA-targeted CAR-T cell therapy for treating this case. In a pivotal testing, 128 patients with multiple myeloma who had failed multiple treatment regimens were treated with Abecma, of which 73% produced an objective response and 33% achieved complete remission [11]. Despite the promising this therapy in multiple myeloma, the persistence of therapeutic effects remains a challenge. Researchers are trying to overcome the problems of target loss, immune escape, and the inability of cells to remain in patients for extended durations.

4. Current Status of Research and Future Development Trend

4.1. Progress and challenges in CAR-T Cell Therapy

In recent years, great progress has been made in this therapy, but as the clinical application of the therapy has been gradually promoted, scientists are aware of its limitations and potential problems, especially its limited application in the treatment of solid tumours. In addition, serious pains remain key barriers to further dissemination of the therapy.

4.2. Innovations and future directions

In view of this, researchers are exploring a variety of new CAR design strategies to augment their safety, performance, and practical application. Current research is focused on optimizing the design of CAR-T cell therapies, improving their efficacy in solid tumours, developing 'existing' allogeneic CAR-T cells, and combining CAR-T therapies with other therapies. With these strategies, researchers hope to overcome the limitations of existing these therapies and expand their application to more cancer types. Firstly, the structural design of this therapy is continuously being optimized to overcome problems such as immune escape and tumour antigen loss. Current research has seen the emergence of bispecific CAR-T cells, which are capable of recognizing two different tumour antigens at the same time, thereby improving their target specificity and reducing the risk of recurrence associated with antigen loss.In addition, researchers have introduced a "suicide switch" into the CAR structure, which allows CAR-T cells to be rapidly inactivated by an external control mechanism in the event of complication, thus enhancing security of the therapy [12]. Secondly, this will also face many more difficult challenges, such as hands-on practice in solid masses. Unlike hematological malignancies, solid masses have a more complex microenvironment that contains a large number of inhibitory cytokines and immunosuppressive cells, which greatly impede the penetration and activation of CAR-T cells.In addition, solid tumours typically exhibit antigenic heterogeneity and low antigen density, which further diminish the efficacy of cells.To address these challenges, experimenters are developing CAR-T cells that can resist the inhibitory tumour microenvironment, such as gene editing to desensitise CAR-T cells to inhibitory signals, or designing CAR structures that can reverse inhibitory signals [13].Another research direction that has attracted much attention is the development of allogeneic CAR-T cells.Most current therapies rely on the patient's own T cells, which results in a cumbersome, costly and lengthy treatment process. To address these issues, researchers are exploring the use of T cells from healthy

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donors to produce "off-the-shelf" CAR-T cells by removing molecular markers that may trigger graft-versus-host disease (GVHD) through gene editing. This method is expected to significantly lower the cost of treatment, increase accessibility of this cell therapy.

4.3. Combinations therapies and expanded applications

The development of combination therapies is an important future direction for this therapy. Many scientists have experimented with it and found that when used alongside other therapies such as PD-1 inhibitors and radiotherapy, may further improve treatment efficacy and reduce tumour resistance to single therapies. For example, PD-1 inhibitors can lift the immunosuppression within the mass's environment, thus enhancing the killing activity of CAR-T cells, whereas chemotherapy or radiotherapy can create better conditions for them to do their job by reducing the tumour volume or destroying the immune escape mechanism of tumour cells [14]. Overall, CAR-T cell therapy research is promising, but also challenging. Due to the continuous improvement of biotechnology and gene editing technology, CAR-T therapies will be more diverse and personalized in future clinical applications. In the future, researchers will continue to explore ways to increase the efficacy of the it, reduce patients' paints and expand its use in more cancer types.

5. Conclusion

The emergence of CAR-T cell therapy marks a major progress in the immunotherapy of hematological malignancies, and its remarkable efficacy has been proven in acute lymphoblastic leukemia, large B-cell lymphoma and multiple myeloma. By genetically modifying T-cells so that they can kill tumor cells, it has brought new light to many individuals with recurrent hematological tumours that have failed to respond to conventional treatment. However, the side effects have become obstacles to its further dissemination. Research in recent years has focus on optimizing CAR design to improve safety and efficacy, in particular by developing bispecific CAR-T cells, introducing suicide switches, and other strategies to counter antigen loss and immune escape. In addition, the application of it in solid tumours faces problems such as microenvironmental inhibition and antigenic heterogeneity, for which researchers are exploring means such as gene editing and signal modulation to enhance its role in complex tumour environments. And improvements in allogeneic CAR-T cells represent progress to increase accessibility while reducing treatment costs. The exploration of combination therapies has also demonstrated the potential for CAR-T therapy to synergise with other immune checkpoint inhibitors, radiotherapy or chemotherapy. In conclusion, although this therapy has made remarkable achievements in hematological malignancies, its future development will depend on further technological innovation and clinical research. Along with increasing advances in biological and gene editing technology, CAR-T therapies are look forwards to achieve more diverse and personalized clinical applications in the coming years, bringing hope for long-term treatment to patients with more cancer types.

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