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Car-T cell therapy: T-immunotherapy application in blood cancer

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Abstract. Considering the unsuccessful results and lack of sustainable efficiency of previous cancer therapies, T-immunotherapy's clinical success has led to a revolution in cancer treatments. Blood cancers, characterized by abnormal blood cells and metastasis, result in severe health issues and cause high mortality rates. Conventional treatments like chemotherapy and radiation often result in poor prognoses due to cancer cell resistance and have a high relapse rate. This paper focuses on how Chimeric Antigen Receptor (CAR)-T cell therapy removes tumor cancerous cells with genetically engineered T-cells. The specific targeting ability of T-cell allows it to overcome the difficulty unresolved by traditional treatments. Despite its significant progress, CAR-T cell therapy also experienced new challenges brought by its specific treatment: cytokine release syndrome and logistical complexities. This paper provides a comprehensive review of T-cell therapy's novel enhancement of blood cancers, including its mechanisms, applications, and side effects after therapy. Various data underline T-cell therapy's potential as a novel cancer treatment, though further research is needed to address its limitations and improve patient outcomes. This research paper provides valuable insights into CAR-T therapy application, minimizing toxicity, and expanding its applicability, offering a reference for future research. Unresolved issues such as managing side effects and improving accessibility continue to be focused for future investigation.

Keywords: Car-T therapy, T-immunotherapy, cytokine release syndrome.

1. Introduction

The successful application of T-immunotherapy in clinical trials since 2017 provides a new possible treatment for cancers that have exhausted all prior therapies and surgical options. Hematologic cancer disrupts the production and function of blood cells and is marked by abnormal cell proliferation and metastasis, leaving tumors throughout the body. Despite blood cells' vital role in human life, blood cancer easily leads to symptoms such as fatigue, weight loss, frequent infections, and death in later stages. Blood cancer has a high degree of heterogeneity, resulting in various subtypes of the same cancer in different patients. This diversity makes it challenging to create effective treatments for each individual. Although chemotherapy and radiation therapy have ability to cure blood cancer, they often result in unresolved issues that lead to poor prognosis due to the cancer cells' high resistance. Low duration of surgery effect often leads to cancer relapse, which, along with poor prognosis, causes low rates of long-term survival for cancer patients.

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T-cell therapy predominates from a prior risk-based combination of surgeries. It outlines a groundbreaking approach in using human's own immune system to kill cancer cells by recognizing and attacking them. Chimeric antigen receptor T-cell therapy is known for programming and training T-cells to target specific tumor antigens in the patient's body. The patient's blood will retain and distribute reprogrammed T-cells, resulting in long-lasting remission and accurate cancer elimination. CAR-T therapy has shown remarkable results among patients with B-cell acute lymphoblastic leukemia who are refractory. US Food and Drug Administration (FDA) data demonstrating an overall remission rate of 82.5% for Tisagenlecleucel, the first CAR-T therapy licensed by the FDA, surpasses the poor response rate of alternative medicines under the same experimental setting, demonstrating the drug's efficacy [1, 2].

Data from a clinical trial show the significance of T-cell therapy in treating blood cancer. Further research about its application for solid tumors has revealed its potential to effectively treat other life-threatening disorders as well. The presence of a suppressive tumor microenvironment that leads to T-cell exhaustion was previously believed to make T-cell treatment in solid tumors unfeasible. However, recent research in extracellular acidosis indicates that acidic environments can eliminate T-cell dysfunction, preserve T-cell stemness, and improve therapeutic outcomes [3].

Despite its progress in promising blood cancer cure, its side effects include CRS, neurotoxicity, and logistical complexities. According to FDA data on Tisagenlecleucel clinical trials, 84% of subjects experience Grade 3 or 4 adverse events [4]. This possibility of severe illness restricted patients from living close to a certified center. Moreover, CAR-T therapy's personalized autologous T-cells set strict patient selection, which limits the accessibility of CAR-T therapy.

Given vast research and clinical endeavors focusing on refining present therapeutic potential, T-cell immunotherapy is a significant approach for treating patients with malignant tumors. This comprehensive review recaps T-cell therapy's revolutionary advances in blood cancer treatment. It elucidates hurdles toward novel targets and strategies, particularly how recent research has made treatment feasible in solid tumors. The discussion will address therapeutic challenges like overcoming resistance, limiting CRS side effects, and progressing efforts to resolve unmet needs to expand therapeutic potential. Ongoing research focuses on optimizing efficacy, minimizing toxicity, and expanding the range for T-cell Therapy use.

2. Mechanism

2.1. Blood Cancer/hematologic malignancy

Platelets, white blood cells, and red blood cells are formed from matured stem cells. This transformation can be observed in bone marrow and lymphatic system. These blood cells are essential for the human body as they transport oxygen around the body, participate in immune responses that fight off infections, and prevent bleeding by clotting scars. When the production of blood cells is impaired and blood cells start behaving abnormally, one is considered to have blood cancer, also known as hematologic malignancy. The primary types include leukemia, lymphoma, and myeloma, each impacting different blood and immune system components. Cancer is diagnosed when abnormal blood cells start replicating and interfering production of normal blood cells, leading to severe health complications. Lymphoma affects the lymphatic system, particularly the lymph nodes and lymphocytes, producing abnormal lymphatic cells that dysfunctions the immune system. Myeloma, on the other hand, is developed in plasma cells, disrupting the production of antibodies and weakening the body's ability to fight infections [5].

2.2. Formation and harmfulness in human body

The specific causes of blood cancer are not fully understood, but research shows that genetic mutations and some environmental factors can induce malignant transformation of normal blood cells. These factors include environmental exposure, radiation, certain chemicals, and genetic predispositions. Cancerous blood cells proliferate without limits by avoiding apoptosis and evading immune system

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attack. Unrestricted proliferation affects the production of stem cells and disrupts the formation process of blood cells, thereby affecting the body's circulation and function. Hematopoietic dysfunction results in symptoms such as anemia, increased susceptibility to infection, and impaired coagulation.

As the disease progresses, blood cancer cells can spread to other organs, further disrupting system function. Malignant tumors metastasize through the blood circulation and continue to expand in other locations, leading to systemic tumors. Blood cancers often infiltrate vital organs such as the lungs, liver, and central nervous system, causing life-threatening complications. The seriousness of blood cancer and its complications is that it originates in the bone marrow and weakens the immune system by preventing the production of normal white blood cells. Therefore, a weakened immune system is incapable of combating the cancerous cells circulating in the patient's body without external intervention.

2.3. T cell-regulated immune response

T-cells, also known as T-lymphocytes, are generated inside bone marrow, thymus glands, and lymphatic systems. T-cells have a vital function in the human immunological system. T-cell is activated when antigen target receptor binds to the correct major histocompatibility complex (MHC) on tumor cells. MHC is evidence for antigen presentation, where MHC was left on the cell's surface after the antigen intruded and disrupted the normal cell process. The T-cell binds to the MHC; this attachment is vital because T-cells only react to the intruder with specific MHC [6]. There are two types of T-cells and MHC molecules that match. Cytotoxic T-cells directly kill infected and cancer cells by themselves; The CD8 receptor on cytotoxic T-cells, or CD8+ cells, specifically interacts with MHC-I. Helper T-cells trigger an immune response by sending a signal to other immune cells; The CD4 receptor on helper T-cells selectively interacts with MHC-II. When the correct attachment between the T-cell and MHC is present, the T-cell activates, triggering an immune response based on T-cell variety. Cytotoxic T-cells directly kill antigen-presenting cells (APCs) by releasing cytotoxins that induce cell death in these compromised cells. Vice versa, helper T-cells, or CD4+ cells, send signals to surrounding cells when antigen is detected. They coordinate this immune response by attracting cytotoxic T-cells, B-cells, and macrophages to attack the pathogens.

3. CAR-T current application

Adoptive immunotherapy, a revolutionary method that strengthens and uses the body's immune system, has been focusing on T-cells in recent times to effectively fight blood malignancies. One such innovation of T-cell is CAR-T therapy. The effectiveness of T-cell-based therapies lies in their ability to provide a targeted immune response. With T-cell's recognition of MHC, CAR T-cells bind to APCs with high specificity, leading to their targeted destruction. This method has demonstrated remarkable success, specifically in hematologic cancer large B-cell lymphoma and hematologic cancer B-cell acute lymphoblastic leukemia, yielding high remission rates and durable responses, offering potent treatment options for malignancies that have proven refractory to conventional treatments.

CAR-T cell therapy has provided new possibilities for cancer treatment by providing customized solutions to the specific subtypes matching an individual's needs. This procedure involves extracting blood from patient, isolating the T cells, and reintroducing the programmed T cell back into the patient's system [7]. Initially, the patient's T cells are harvested through leukapheresis. Following extraction, these T cells undergo genetic modification within a laboratory setting. Scientists introduce a new gene onto the T cell's surface using a viral vector. The gene encodes for a chimeric antigen receptor specific to the patient's cancer. T-cells, after modification, will be replicated and reinserted into the affected individual's body. Once inside, they specifically identify and destroy tumor antigens. [8]. Unlike traditional treatments, which cause collateral damage to normal tissues and lead to significant side effects, T-cell therapies specifically target malignant cells. This precision reduces collateral damage and improves the overall outcomes for patients. The lock between MHC and T-cells acts as specific markers that only target antigens present exclusively on the surface of APCs, sparing normal tissues. Furthermore, ongoing research is focused on enhancing the efficacy and safety of these therapies, expanding their

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applicability to a broader range of hematologic malignancies, and improving the quality of life for recipients.

Tisagenlecleucel (Kymriah) is one of many FDA-approved therapies using CAR-T. This therapy is designed for young adult and pediatric patients up to 25 years old who have relapsed or refractory B-cell acute lymphoblastic leukemia, as well as for adult patients experiencing relapsed or refractory diffuse large B-cell lymphoma that had previously taken two lines of conventional treatments [8]. In the case of Kymriah, the CAR is tailored to target and suppress CD-19, which is frequently present on the surface of B-cell malignancies, presenting APCs. After the addition of transgene encoding to the patient's CAR-T cells, the cells are expanded or replicated in the laboratory [8]. This process typically spans several weeks. Kymriah CAR-T cells include three domains: CD3-zeta signaling domain, antigen binding (CD-19) domain, and 4-1BB costimulatory domain. Once inside the recipient's body, anti-fragment chains in CAR-T cells actively seek out and bind to tumor cells expressing their target: CD19 antigen [8]. CD3-zeta signaling domain works as a T-cell activator and initiates following antitumor behavior [8]. Upon binding, the CAR-T cells activate and initiate a highly targeted immune response against the cancerous cells. They release cytotoxic molecules and prompt other immune cells to join the immune reaction toward B-tumors. Additionally, a subset of infused CAR-T cells may differentiate into memory T cells, ensuring long-term immunity, where the costimulatory domain plays its role. 4-1BB costimulatory domain enhances the expansion and persistence of tisagenlecleucel, allowing Kymriah treatment to guarantee a lifetime cure [9]. Sometimes, CD-19 CAR-T cells' costimulatory domain is encoded with a CD28 instead, which correlates with effector memory T-cell differentiation, also providing persistence of immune efficiency of therapy [9,10].

4. CAR-T side effects - Cytokine release syndrome

CRS is one of the top life-threatening side effects led by CAR-T cell therapy and occurs in up to 100% of patients [11]. CRS occurs due to CAR-T cells' rapid and massive activation upon encountering their target antigens on cancer cells. This activation leads to cytokines release, particularly interleukin-6 (IL-6), along with other inflammatory molecules like IL-1, interferon-gamma (IFN-γ), and TNF-α [12]. These cytokines are essential for the immune response, but excessive release can trigger an inflammatory response, resulting in CRS. The severity of CRS ranges from mild to severe and is common in CAR-T therapy receivers. Different costimulatory domains contribute differently to cytokine release syndrome. Patients receiving 4-1BB-costimulated CAR-T cell therapy typically develop cytokine release syndrome at a later stage compared to patients receiving CD28-costimulated CAR-T cell therapy [13]. However, the CRS symptoms tend to last longer in the previous group [13]. CD28-costimulated CAR-T cells expand more rapidly than 4-1BB-costimulated CART cells [14]. Clinical manifestations of CRS typically include high fever, chills, hypotension, rapid heart rate, hypoxia (low oxygen levels), and multi-organ dysfunction, affecting organs such as the liver, kidneys, and lungs [15].

The incidence of CRS varies depending on several factors, including specific CAR-T products, the type of cancer being treated, and the dose of CAR-T cells. Studies have reported that CRS has 100% occurrence in some CAR-T 19 clinical trials, with severe cases (grade 3 or higher) occurring in approximately 20-30% of patients [4,11]. The management of CRS is crucial for patient safety and involves both supportive care and targeted treatments. Supportive care includes measures to stabilize vital signs and organ function, such as intravenous fluids, oxygen therapy, and vasopressors for blood pressure support. For severe cases, specific interventions include the administration of tocilizumab, which can effectively reduce the levels of IL-6 and mitigate the inflammatory response [11,15]. Corticosteroids may also be used to dampen the immune response if tocilizumab is insufficient or contraindicated [16]. Despite CRS's high incidence and severity, prompt recognition and treatment have significantly improved patient outcomes, allowing many to benefit from the transformative potential of CAR-T therapy.

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5. Possible improvements of current CAR-T cell therapy

Scientists are actively exploring various strategies to reduce T cell therapy side effects, particularly CRS. One approach involves advancements in cytokine management strategies, such as cytokine blockade or the use of cytokine scavengers, which are being explored to mitigate the systemic inflammation associated with CRS. Studies suggest that IL-1, generated by activated macrophages, significantly contributes to triggering CRS. Anakinra, an IL-1 antagonist currently clinically available but awaiting FDA approval for CAR-T-associated toxicities, shows potential in reducing CRS following CAR-T cell therapy [17]. This suggests that Anakinra could be effective in mitigating the inflammatory responses associated with CRS and alleviating the neurological symptoms observed in ICANS post-CAR-T cell therapy [17,18]. Further studies and clinical trials are necessary to confirm these results and establish the efficacy and efficiency of Anakinra for managing adverse effects related to CAR-T therapy.

6. Conclusion

This review highlights the transformative potential of T-cell immunotherapy, particularly CAR-T therapy, in treating blood cancers. By therapeutic application of the human immune system, CAR-T therapy offers a targeted approach that has shown remarkable success in clinical trials, which underscores its effectiveness compared to traditional treatments. However, the implementation of CAR-T cell therapy also presents significant challenges, including CRS, neurotoxicity, and the complexities of manufacturing and accessibility. These side effects pose significant risks that need careful management. (Furthermore, the logistical complexities and strict patient selection criteria limit the accessibility of this therapy.) Despite these hurdles, ongoing research and clinical efforts aim to refine CAR-T therapy, enhance its safety and efficacy, and improve patient outcomes significantly.

Further investigation of CAR-T therapy into solid tumor application, once considered impossible, shows promising potential, indicating that this therapy could be applicable to a wider range of cancers in the future. Future research should focus on overcoming these limitations, exploring cost-effective solutions, and developing strategies to manage side effects better. The exploration of CAR-T therapy to include solid tumors represents a critical area for future investigation, with the potential to significantly broaden the therapeutic applications of this promising treatment.

However, this study focuses primarily on the CAR-T therapy's current state application in Blood cancer. There are various research topics focusing on how tumor microenvironment affects T-cell survival in solid tumors, hoping to overcome this difficulty; these research are not explored in detail. The rapid development of CAR-T cell therapy, especially in the context of its application to solid tumors and other diseases, presents a significant challenge in comprehensively covering all aspects of this dynamic field. Consequently, this research paper does not include all emerging findings and ongoing studies, which could provide further understanding of the potential and limitations of CAR-T therapy.

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