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CAR-T Therapy in Leukemia: Limitations and Prospects

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Abstract. In the broad field of cancer management via immunotherapy, chimeric antigen receptor T-cell therapy (CAR-T therapy), commonly known as CAR-T therapy, has become a game-changing approach, particularly for patients with relapsed or refractory lymphoma. Using genetic engineering, a patient's T cells can be genetically modified to target specific tumor antigens allowing CAR-T cells to identify and destroy abnormal cells, which can provide long-term anti-tumor responses. The mechanisms and clinical applications of CAR-T therapy in leukemia, particularly in B-cell ALL and CD19-targeted CAR-T therapy will be discussed in this thesis. While CAR-T therapy shows great promise in its therapeutic ability, it faces a number of critical challenges, including insufficient efficacy against solid malignancies, on-target off-tumor effects, cytokine release syndrome (CRS), and the cost and complexity of individualized production. To overcome these issues, investigators have investigated innovations aimed at enhancing CAR-T cell stability, infiltration into tumors, and anti-tumor efficacy, such as the creation of IL-7/XCL1-armed CAR-T cells. Additionally, outcome-based reimbursement programs could help to reduce some of the financial barriers associated with CAR-T treatment. To conclude, CAR-T therapy represents a potential breakthrough in lymphoma treatment, while continued research into safety, persistence, accessibility, and cost-effectiveness is crucial to further improve the medical benefits.

Keywords: Restrictions, CAR-T therapy, Prospects

1. Introduction

Leukemia is a group of hematological cancers in which there is an overproduction and accumulation of immature or abnormal bone marrow cells in the bone marrow and peripheral blood. Leukemic cells may have genetic changes that prevent cells from maturing, growing and living the normal lifespan, leading to uncontrolled growth of the malignant cells. These types of genetic defects could affect genes responsible for regulating transcription, intracellular signaling pathways and cell specification. Changes in these biological pathways may therefore make it easier to develop and progress different types of leukemia. Therefore, the lethality of leukemia varies significantly based on pathological features; for example, chronic lymphocytic leukemia (CLL) 5-year survival rate is 88.5%, whereas Acute myeloid leukemia (AML) 5-year survival rate is 31.9% [1].

Today, standard modalities like cytotoxic agents, targeted molecules and hematopoietic stem cell restoration have significantly improved patients' life span. However, many people may develop

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resistance to the treatment or may have a recurrence after a successful initial treatment. Because of these limitations, increasing attention is being paid to more advanced approaches aimed at selectively identifying and killing abnormal cells. One type of immunotherapy, called chimeric antigen receptor T-cell (CAR-T) therapy, has emerged as a promising treatment. In this schema, the person's own T cells are genetically modified to recognize specific antigens found on cancerous cells.

CAR-T immunotherapy has become a cornerstone in the oncology field, particularly for the treatment of leukemia and other haematological malignancies. This treatment consists of modifying T cells from the patient with a synthetic chimeric antigen receptor (CAR), which enables the modified T cells to recognize and destroy cancerous cells more effectively. From the start, CAR-T treatment has demonstrated great potential in patients with relapsed or resistant hematological disorders and can be used as an additional therapeutic option for patients who have few treatment alternatives. However, this strategy has been shown to have serious side effects and other challenges that could affect its effectiveness and access. Despite the success of CAR-T therapy for the management of leukemia, it is still not a major public concern. Hence, this study focuses on the use, challenges, and limitations of CAR-T in the treatment of leukemia.

2. Mechanism

In the beginning, CAR-T immunotherapy is a key step forward for cancer therapy; it is a process by which characteristics of T cells are modified to seek out and destroy cancerous cells. Although significant progress has been made in the application of conventional CAR-T techniques to the treatment of hematological malignancies, the practical implementation of these techniques is limited by a number of challenges such as limited persistence, reduced tumor penetration, and reduced CAR-T activity in the complex tumor environment. The ability of CAR-T therapy to recognize targets antigens outside of the context of normal antigenic presentation is a key factor in overcoming some of the limitations. CARs differ from classical T-cell receptors (TCRs) in that they bind directly to extracellular markers, and do not require MHC mediated presentation. CD3ζ module and other costimulatory signals (like CD28 or 4-1BB) mediate T-cell activation when they encounter the specific target antigen. The engineered CAR-T cell then proliferates, secretes cytokines and kills the targeted tumour cell by perforin and granzyme etc.

Because of the high and consistent expression of recognizable surface markers on these aggressive leukemic cells, CAR-T treatments are very potent against leukemia. CD19 is, for example, highly expressed by malignant B lymphocytes, and is a key target of CD19-based CAR-T therapy. In addition, leukemia cells are found mostly in the bloodstream and bone marrow and are much more accessible than tumour cells in solid cancers. The potent anti-leukemic activity of CAR-T cells in subsets of leukemia is, in part, due to the availability of distinct target antigens, the ease of access to malignant cells and the ability of CAR-T cells to expand and persist in the organism.

3. Applications in hematological malignancies (leukemia)

In the real world, the delivery of CAR-T treatment is mainly in leukemia, with an impressive clinical effect on B-cell acute lymphoblastic leukemia (B-ALL). So, CARs against CD19 are made by genetically engineering a human T cell to produce them in vitro and then putting them back inside the patient. For example, based on FDA, tisagenlecleucel, a CD19-directed genetically engineered autologous T-cell immunotherapy, is prescribed for patients up to twenty five years of survival with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

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and the consequences of CAR-T therapy in B-ALL is prominent [2]. Shown by the National Cancer Institute, this trial demonstrates that using T cells engineered to target CD19 in treatment-resistant cases of pediatric and young adult B-cell ALL is associated with strong anti-leukemia effects [3].

CAR-T therapy targeting the CD19 antigen has led to a significant transformation in the treatment of adult patients with relapsed or refractory [4]. There is also a wealth of evidence of the effectiveness of CAR-T therapy in B-cell acute lymphoblastic leukemia (B-ALL), particularly when the cancer cells express CD19. In the pivotal ELIANA trial, 81 percent of 200 children and adolescents with relapsed or resistant B-ALL achieved remission 3 months after being given the CD19-targeted CAR-T product tisagenlecleucel. In all responders, there was minimal residual disease (MRD) negativity as the intervention was effective in clearing the leukemia cells to the extent that MRD assays could not detect. Moreover, CAR-T therapy is not only effective in reducing the leukemia burden, but also induces long-lasting effects in several patients. Some people may go into complete remission from just one treatment. In the ELIANA study, among patients who responded, relapse-free survival was approximately 80% at 6 months and 59% at 12 months; CAR-T cells could also persist in the blood for as long as 20 months [5].

A type of malignancy, acute lymphoblastic leukemia (ALL), is a specific type of leukemia in which the cells that multiply are malignant lymphocytes and in which many B-ALL cells have the CD19 marker. This makes CD19 a key target of CAR-T, which can find and destroy CD19+ leukemia cells. Research shows that there is higher remission rate in B-ALL patients and investigators are exploring other possibilities, such as CD22, CD20, CD7 and CD5. In addition, there is a growing development of multi-target CAR-T approaches to reduce the risk of antigenic escape and prolong the therapeutic effects.

In contrast, while detection of CD19 on CLL B lymphocytes has been discovered, CAR-T treatments have been less promising in the treatment of CLL. One possible explanation is the severe immune dysfunction that occurs in CLL. Changing T-cell proliferation, immune synapse formation, and killing activity, for example, could lead to decreased function and effectiveness of genetically engineered CAR-T cells. Therefore, in addition to the availability of a suitable tumor antigen, the efficacy of CAR-T therapy depends on the status and function of the patients' innate immune system. Further studies are still needed to do more to improve the persistence of CAR-T cells, reduce T-cell exhaustion, and create more effective targeting strategies that could potentially extend the benefits of CAR-T beyond different leukemia subpopulations. This could be a potential application in elderly patients with comorbidities as a therapy with less adverse events compared to an allogeneic transplantation [6].

The ELEANA Phase II study is a 5-year follow-up study that included 79 pediatric and young adult patients with relapsed/refractory B-ALL. Follow-up was done for a mean of 79.4 months. Tisagenlecleucel was administered as a single infusion; for patients with a body weight of ≤ 50 kg dosage was based on body mass index. 70 patients (88.6%) reached the CR/CRi. 65 patients went into remission in 3 months. For the intention-to-treat analysis, the 5-year relapse-free survival was 47.3% (with transplantation censored) and 51.0% (without transplantation censored); the median overall survival had not been reached and the 5-year overall survival was 55.0% and 62.4%, respectively. Recurrence-free survival (RFS) was better in patients who received a dose higher than the median. The 5-year RFS for the ≤ 50 kg group was 71.1% vs. 41.9% for the < 50 kg group, and 72.9% vs. 11.4% for the > 50 kg group. Long-term safety was manageable, with only 1 case of secondary malignancy, and no secondary T-cell malignancies. This supports its use as a definitive treatment for some patients [7].

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4. Limitations

One major limitation of CAR-T therapy is that it is not very effective against solid tumors. Unlike AML, solid tumors have more complicated biological structures and microenvironmental characteristics (TME) that make it less accessible for CAR-T cells to infiltrate and kill malignant cells. This solid tumor microenvironment comprises immunosuppressive substances and regulatory cells that may inhibit immune responses. For instance, tumor-infiltrating macrophages and regulatory signaling factors might diminish the effectiveness and stability of CAR-T cells. These factors can create an environment conducive to CAR-T cell exhaustion, limiting their ability to effectively persist in targeting cancerous cells.

Solid malignancies are characterized by abnormal vascular organization and a large amount of ECM which serve as mechanical barriers and impair movement of immune cells. As a result, CAR-Ts could potentially recognize tumor associated epitopes, but still face challenges in penetrating the tumor and reaching target cells. In addition, antigen heterogeneity is a major challenge with solid neoplasms. The subsets of cells in a tumor can express different epitopes, or different levels of the same epitope. CAR-T cells targeting specific epitopes may find extremely low or undetectable amounts of epitopes on the surface of malignant cells. Such antigen-negative cells could thus evade CAR-T-mediated destruction, endure the therapy, and possibly facilitate tumor relapse. For instance, reflecting a slower pace of commercialization of CAR-T cell therapy in solid tumors compared to hematologic malignancies [8].

Additionally, even though the CAR-T cell therapies are designed to selectively target malignant cells, off-target phenomena are still a major risk. This could occur if the antigen targeted by the CAR-T cell is also present on normal cells, which could be targeted by the CAR-T cells as well. The chance depends on the antigen selected, as many tumor associated antigens are only partially different from those associated with normal tissues and could be found in lower amounts in normal tissues. If CAR-T cells mistakenly target these normal cells, they can cause serious damage to the cells.

A pertinent issue referred to as "on-target, off-tumor" toxicity arises in such scenarios. In this situation, CAR-T agents are able to target their target antigen, but the same antigen also exists on non-tumor tissues. For example, CD19 is expressed on malignant B cells making it an excellent target for CD19-targeted CAR-T therapy in B-cell tumors. However, CD19 is also found on normal B cells, which means that CD19-targeted CAR-Ts could also attack these true B cells. As such, selecting a specific antigen could optimize CAR-T cell targeting ability of CAR-T cells against malignancy but also presents a major safety concern due to the presence of the same antigen on normal organs.

A major flaw of CAR-T therapy is that, at times, the immune response against the cancer cells is too strong, causing a condition known as "cytokine release syndrome" or CRS. On encountering tumor-specific epitopes, CAR-T cells get very activated and produce huge amounts of signaling proteins called cytokines. These cytokines can recruit and activate other immune cells, such as macrophages, to produce more pro-inflammatory cytokines, such as interleukin-6 (IL-6). This can create a vicious cycle of inflammation as the activated CAR-T cells activate macrophages which then secrete more cytokines, which in turn further stimulate the entire immune system.

For example, if the patient has B-cell acute lymphoblastic leukemia (B-ALL), the cells could trigger a strong immune response because of their strong binding with CD19-targeting CAR-T cells. This activation of the immune system is very important to get rid of the malignant cells, but may also lead to CRS if it is too strong. This state is accompanied by fever and systemic symptoms, and

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can lead to hypotension and hypoxia in more severe cases. Factors such as the size of the tumor, the number of CAR-T cells administered, and the type of immune activation can greatly influence the severity of CRS. Thus, CRS is a major limitation of CAR-T: the vigorous immune response that allows CAR-T cells to produce strong anti-tumor effects could also be responsible for overwhelming immune responses that cause severe toxicity in CAR-T therapy. To everyone's surprise, real-world data suggested that cytokine release syndrome (CRS) among chimeric antigen receptor (CAR) T-cell therapy recipients with hematologic malignancy occurred among 56.2% to 71.7% of patients, according to results of a study that were presented at the ASH Annual Meeting 2023 [9].

Fortunately, CRS can frequently be managed via diligent surveillance and suitable interventions. One of the main treatments is the use of IL-6 receptor inhibitors, which can help to reduce inflammation and manage its symptoms. Researchers are also working on safer methods of CAR-T that maintain the cells' anti-tumour activity but reduce any overstimulation of the immune system.

In addition, manufacturing CAR-T cells requires a high level of expertise, complex laboratory equipment, and precise procedures. There are two FDA-approved products that can be used in CAR-T therapy: tisagenlecleucel, which costs approximately $50, 000 per dose, and axicabtagene ciloleucel, also priced at approximately $50, 000 per dose. This process is very personalized as each person's genetic characteristics vary, and involves a significant amount of time and cost. On the other side, people with late-stage cancers might possess compromised immune systems, which makes it challenging to isolate sufficient normal T cells for effective CAR-T synthesis. Ultimately, the customized nature of CAR-T fabrication can render the entire therapy extremely costly. Expenses concerning cell retrieval, genetic alteration, research expansion, medical admission, and the oversight of possible complications could collectively add to the substantial monetary strain of care and prompt inquiries regarding whether healthcare benefits can offer adequate reimbursement. In the foreseeable future, political debate will be required concerning access to curative treatments either being a privilege for the wealthy or a right for those in need [10].

5. Future perspective

To overcome these challenges mentioned above, investigators have developed the next generation CAR-T paradigm which includes armored CAR-T cells. Unlike the standard CAR-T cells, these engineered cells are further modified to produce proteins that will stimulate the immune system and enhance the T-cell function and longevity. For example, the cytokine IL-7 has been shown to play an important role in the survival, proliferation and maintenance of memory T-cell subsets. IL-7 may help the CAR-T agents to maintain their anti-tumour response for a longer period after the CAR-T intervention by promoting T-cell retention. The chemokine XCL1 is involved in immune cell mobilisation and migration and is thought to aid in the distribution and localization of CAR-T cells in tumour environments. ExCAR-T cells are therefore a modern development in the field of CAR-T. Compared with conventional CAR-T cells (cCAR-T), ExCAR-T cells are engineered to express IL-7 and XCL1 that provide direct functional improvements. These mechanisms directly address the main drawbacks of current CAR-T therapies. Thus, the delivery of IL-7/XCL1 was proposed to be a good strategy for the future development of CAR-T cells, where it might be used to improve their therapeutic efficacy, infiltration and resilience.

Looking ahead, combining IL-7 and XCL1 with CAR-T cells is a potential avenue to further improve CAR-T-based leukemia therapies. Although CAR-T therapy has shown promising improved efficacy in B-ALL, the issues of CAR-T cell exhaustion and relapse remain important obstacles. IL-7 could negate these limitations by enhancing the survival, growth and memory subset maintenance of CAR-T cells, so that they persist for a longer time after injection. At the same time,

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XCL1 may help to improve recruitment and coordination of immune compartments in the leukemia microsphere, including the bone marrow, where there may be residual malignant cells after treatment. This synergy may be able to sustain a larger and more persistent CAR-T pool with enhanced interaction with the surrounding immune environment by IL-7/XCL1-equipped CAR-T cells. Therefore, while further clinical studies are needed to assess how effective and safe IL-7/XCL1 are when used in patients with leukemia, IL-7/XCL1-armed CAR-T cells could be a promising future approach to reduce leukemic relapse rates and prolong the persistence of CAR-T-mediated hematological responses.

Perhaps a way to lower the cost of CAR-T therapy would be through an alternative payment model, such as outcomes-based agreements (OBAs), where a percentage of the payment could be based on achieving certain medical outcomes.

One approach to addressing the very high costs of CAR-T therapy is to offer outcomes-based agreements (OBAs): payment for the CAR-T therapy can be tied in part to the achievement of predefined health outcomes. This concept is already being tested in the U. S. Cell and Gene Therapy (CGT) Access Model. CMS would negotiate with the manufacturers on behalf of participating Medicaid programs such that payments/rebates are dependent on treatment outcomes. The model currently focuses on gene therapies for sickle cell disease, but CMS explicitly says it is exploring additional conditions [11].

6. Conclusion

Thus, CAR-T cell therapy is a representative example of the revolutionary advancement in the treatment of leukemia, particularly in the context of B-cell ALL with relapsed or resistant disease. CAR-T can be genetically engineered to recognize certain tumor epitopes in patients, resulting in strong and often persistent anti-tumor activity. However, there are multiple challenges to its broader use, such as the development of tumor resistance, the variability of antigens, off-target/on-target off-target toxicity, cytokine release syndrome and the tremendous cost and complexity of customized production. These restrictions suggest that improvements to CAR-T therapy will require more than improvements to the ability of the CAR-T to kill the tumor cells; they will also require improvements in safety, persistence, and cost. New approaches, such as the development of IL-7/XCL1-armored CAR-T cells, could potentially improve the stability of the T cells and attraction of immune cells, while reimbursement models based on the performance of a therapy could help address economic challenges. Finally, ongoing research and advancements in CAR-T development, medical investigation, and medical policy might make this option safer, more effective, and more affordable for more patients with leukemia.

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