Advantages and Disadvantages of Car-T Therapy in the Clinical Treatment of Diffuse Large B-Cell Lymphoma (DLBCL)

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Abstract. Chimeric antigen receptor T-cell (CAR-T) therapy is a new innovative cancer treatment. In recent years, many clinical studies have demonstrated its efficacy in the treatment of DLBCL. Compared to many existing cancer treatments, CAR-T therapy offers many advantages. For example, unique specificity and excellent efficacy in patients with refractory and recurrent tumors. This article focuses on the application of CAR-T in the treatment of DLBCL and analyzes the advantages and disadvantages of this therapy from multiple perspectives. The advantages of CAR-T therapy are discussed in three aspects: CAR-T for relapsed and chemotherapy-resistant patients, CAR-T cell's distinctive specificity and ideal treatment outcome. Then, the three most representative limitations of CAR-T therapy are analyzed in this article: antigen escape, antigen-positive relapse, and toxicities. Finally, the article points out the promising future of CAR-T therapy.

Keywords: Car-T Therapy, Diffuse Large B-Cell Lymphoma, Clinical Trial.

1. Introduction

Human lymphomas are classified as Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). NHL includes various subtypes of lymphatic malignancies. These tumours are generated by the clonal growth of T, B or natural killer cells at various stages of development. NK cell and T lymphomas can occur at any stage of normal T or NK cell lymphopoiesis, but B-cell lymphomas typically arise from germinal center or post germinal center B cells. Even though malignant cells have genetic defects, they retain many phenotypic traits of normal cells. Hence, immunotherapy target antigens are frequently expressed on both cancer and non-malignant cells [1].

DLBCL is a common form of NHL. Typical treatments for DLBCL include chemotherapy, radiation therapy, immunotherapy, etc. DLBCL is potentially curable. Most patients with DLBCL respond well to initial treatment such as chemotherapy. However, about 20-30% of DLBCL patients become resistant to chemotherapy and radiation therapy. For instances in patients with refractory/relapsed (R/R) DLBCL after chemotherapy, hematopoietic stem cell transplantation (HSCT) is normally regarded as the next treatment method. Unfortunately, roughly 40% of patients are ineligible for HSCT due to a variety of potential comorbidities, and nearly half of individuals treated with HSCT relapse. This means that this treatment is not effective in patients with R/R disease. Hence, many researchers have worked hard to develop novel therapies to help patients with R/R lymphoma.

Recently, CAR-T therapy has demonstrated encouraging outcomes in the treatment of B-cell cancers. CAR-T cells, unlike regular T cells, identify unprocessed antigens. They identify and eliminate malignant cells independently of the human leukocyte antigen (HLA) system. This trait circumvents the primary mechanisms of tumor escape, such as poor antigen processing and decreased production of class I HLA molecules, which would otherwise preclude detection by HLA-restricted T cells [2].

2. Advantages of car-t therapy

In recent decades, basic cancer treatments have consisted mainly of chemotherapy, radiation therapy, and surgery. To date, these treatments still play a major role in cancer treatment. Meanwhile, many new therapeutic approaches regarding cancer are emerging, such as immunotherapy. There is

hope that these emerging therapeutic technologies will change the treatment landscape for cancer patients. The CAR-T therapy discussed in this article is one of the promising immunotherapies for cancer [2]. The advantages of CAR-T therapy are mainly divided into the following points.

2.1. CAR-T for relapsed and chemotherapy-resistant patients

For R/R patients, CAR-T is currently a novel and effective immunotherapy. Extensive studies have demonstrated that this emerging therapy can provide effective treatment outcomes for individuals with poor prognosis despite multiple chemotherapies. Zhao et al. mentioned a clinical trial on the use of CAR-T for the treatment of R/R lymphoma, which showed that this therapy could well control the spread of cancer cells in patients [3].

The main reason for the efficacy of this novel immunotherapy is that it consolidates the individual's immune system and induces a durable and potent resistance to cancer cells in patients with R/R lymphoma. Thus, this novel immunotherapy has a greater killing effect on cancer cells compared to traditional chemotherapy [2].

2.2. Distinctive specificity

In contrast to many other immune cells, CAR-T cells have the exceptional ability to target and destroy cancer cells that have the particular TAAs. Thus, to a certain extent, CAR-T therapy can prevent the needless destruction of good tissues. Furthermore, CAR-T cells are independent of HLA expression and are capable of recognizing cell surface chemicals. Through the concealment of HLAs or other molecules involved in the processing and presentation of antigens, this trait enables the targeting of malignancies that evade T-cell immune surveillance. Furthermore, The CAR's flexible intracellular signaling domains allow the cell to tolerate both direct and indirect downregulation of co-stimulatory molecules by cancer cells. Potential antigens, including lipid, protein, and carbohydrate antigens, can all be recognized by CAR-T cells [3].

2.3. Ideal treatment outcome

As mentioned earlier, the clinical treatment process regarding DLBCL mainly includes standard combination chemotherapy (RCHOP) and stem cell transplantation therapy. However, these standard treatments are often less effective in patients with high-risk features, such as early relapse within one year, single/double-hit lymphoma, and preliminary refractory disease [2]. In this case, CAR-T therapy has the potential to offer new hope to patients.

The FDA recently approved CAR-T based anticancer treatments for chemoresistant NHL that target the pan-B-cell marker CD19. Since most B-cell lymphomas and all stages of B-cell development exhibit this antigen's expression. Anti-CD19 CAR-T cells were employed on patients who had advanced B-cell malignancies. Four patients with chemotherapy-resistant DLBCL obtained complete remission following treatment (CR). Additionally, other patients with large B-cell lymphomas received injections of anti-CD19 CAR-T cells from different research groups. Following treatment, analysis of the patients revealed that 28% of them displayed partial remission (RP), while 54% were in complete remission (CR) [2].

This new CAR-T-related treatment is now achieving sustainable recovery in 40% of patients with drug-resistant lymphoma who were not previously receiving any treatment regimen. Additionally, individuals with severe lymphoma who relapsed after at least two prior lines of therapy are currently receiving such therapies [2]. Overall, using CAR-T therapy for DLBCL has multiple advantages. Among them, the most valuable is that this treatment offers the hope of complete or partial recovery for many patients with high-risk characteristics.

3. Limitations

Although CAR-T has many advantages mentioned above. However, this novel therapy still has many limitations in clinical application.

3.1. Antigen escape

Undeniably, this novel immunotherapy offers new hope for patients with R/R B-cell malignancies. The two FDA-approved CAR T-cell products are tisagenlecleucel and axicabtagene ciloleucel, both of which have shown very good efficacy in early clinical trials. Unfortunately, follow-up surveys on CAR-T therapy showed that a large proportion of patients relapse due to acquired tumor resistance. This recurrence of B-cell malignancies is usually due to immune stress of CAR-T cells driving cancer evolution by modulating the expression of their target antigens, either by a decrease in antigen expression to a level below the threshold necessary for CAR T-cell activation or a loss of detectable antigen [4].

The tumor resistance to CAR designs that target a single antigen is one of the most difficult limitations of this innovative treatment. Despite the initial excellent response rates that single antigen-targeted CAR-T cells can offer, in a sizable portion of patients who get this therapy, the expression of the target antigen in the malignant cells is completely or partially lost. Antigen escape is used to describe this partial or whole lack of target antigen expression. Even though CD19-targeted CAR-T therapy cures 70–90% of patients with relapsed or resistant acute lymphoblastic leukemia, follow-up data in recent years have revealed common disease resistance mechanisms, including loss/downregulation of CD19 antigen, in the 30%–70% of patients with relapsed disease after treatment [5].

In recent years, many clinical trials on NHL have also confirmed that CAR-T therapy is not always effective. Eight adult NHL patients were evaluated in one clinical trial, and it was discovered that six of them had a CD19-negative illness that rendered them resistant to the CD19 CAR-T therapy. Three of the eleven NHL patients whose tissue was examined in another clinical trial and treated with CD19 had immunohistochemical evidence of CD19 deletion. Target antigen loss does occur in targets than CD19, such as BCMA, EGFRvll, and IL13R2, albeit the incidence is still unknown [4].

Researchers have identified two pathways of CD19 antigen escape—antigen downregulation and lineage switch—by examining patients with B-ALL. Researchers discover that patients with antigen downregulation express additional CD19 splice variants, such as Δexon-2 and Δexon-5,6, instead of the expected exon splice. The Δexon that encodes a CD19 extracellular recognition epitope is absent from Δexon-2, and the transmembrane domain is absent from Δexons 5 and 6. A patient who lacks the expression of the CD19 chaperone protein, CD81, was also discovered in a clinical trial. Hence, each of them will result in the surface target's expression level being lower. In these situations, CAR-T therapy would put the patients under immune selection pressure, causing them to express more alternative CD19 splice variants. As a result, antigen loss is accelerated. Researchers demonstrate how the lineage flip will cause phenotypic changes akin to switching from lymphoid to myeloid to escape the treatment. One outstanding illustration comes from a clinical experiment in which the medication caused the cells of a chronic lymphocytic leukemia (CLL) patient to change into a plasmablastic lymphoma that is related to clones [4].

3.2. Antigen-positive relapse

One of the primary causes of CAR T-cell therapy resistance is targeted antigen-positive relapse. A 2018 study found that among DLBCL patients, the proportion of CD19-positive relapses was nearly 60% (14/21). The target antigen-positive relapse is connected to the CAR T-cell abnormalities, the researchers suggest, even if the precise mechanism is still unknown. The signals involved in this process, such as TNF-related apoptosis-inducing ligand, Fas ligand, and interferon, play a crucial role in CAR-T cells' ability to recognize antigens and induce tumor cell apoptosis. This leads the researchers to the conclusion that altering tumor cells' survival or apoptosis is how tumor antigen-positive CAR-T treatment resistance is obtained. The hypothesis was supported by an experiment. The sensitive cells were treated in the experiment using a TRAIL inhibitor in combination with CAR-T, and the results showed that the cytotoxic effect of CAR-T cells is inhibited, and tumor antigen-positive resistance is identified. Researchers also note that target antigen-positive resistance can be caused by tumor mutations in PTEN and JAK1/JAK2, but the mechanisms are still unknown [6].

3.3. Toxicities

CAR-T cell toxicity is also a major challenge in clinical application. These severe cytotoxicities have, to some extent, contributed to the inability of the therapies to be widely used [2].

3.3.1 Cytokine release syndrome (CRS)

CAR-T Treatment may result in severe side effect known as CRS. CRS is caused by the proliferation and activation of T cells resulting in elevated cytokine levels in the body, which in turn produces a systemic inflammatory response [7].

The clinical symptoms associated with CRS are diverse and usually evolve with the progression of the disease. Patients experiencing CRS usually first develop fever a few hours/days after receiving CAR-T cell injections. A clinical trial conducted by Brudno and Kochenderfer found that patients could develop fever as early as the day of CAR-T cell injection and as late as usually the ninth day after injection. Additionally, in a very small number of cases, the symptoms associated with CRS did not appear until the 14th day after the injection. Patients who develop CRS may present with a range of other symptoms after exhibiting high fever. For example, decreased cardiac function, sinus tachycardia, and hypotension [8]. Clinical symptoms of CRS are individually variable, ranging from a self-limiting mild inflammatory response (e.g., muscle pain and fever) to life-threatening severe conditions [7]. In a clinical study that included 30 patients with CRS, researchers found that most patients had mild to moderate symptoms (22 in total). This group of patients required hospitalization primarily for febrile neutropenia. The remaining minority of patients (7 in total) had severe CRS-related symptoms, such as severe dyspnea and coagulation disorders [7].

In the years since CAR-T cells were used in oncology treatment, extensive clinical studies have demonstrated that CRS induced by CAR-T cells exhibits a very diverse range of symptoms in different individuals. Researchers believe that the diversity of symptoms occurs because of the patients' own physical conditions. For example, individual immune status, IL-6 levels, peak CAR T cells, tumor load, and gut bacterial environment. Besides, understanding these factors that influence the symptoms displayed by CRS may help us to find better ways to manage the condition of CRS patients [9].

3.3.2 Encephalopathy

Some studies indicate neurotoxicity of CAR-T therapy, meaning that this treatment modality may also have adverse neurological effects. The encephalopathy caused by such therapy is referred to as CAR-T cell associated encephalopathy syndrome (CRES). Patients experiencing CRES may exhibit highly diverse neurological complaints. Examples include language dysfunction, ataxia, tremor, cognitive impairment, neurological paralysis, and somnolence. Since CAR-T cell induced, neurotoxicity is not limited to the central nervous system but causes widespread neurotoxicity in the brain [8]. In most cases, the symptoms related to neurotoxicity caused by CAR-T cells are self-limiting and can gradually subside within two to three days after the onset of the disease [7].

It is noteworthy that CRES-related symptoms may occur simultaneously with the CRS symptoms mentioned above. Moreover, extensive clinical experience points out that neurotoxicity may happen as soon as the second day of cell injection and as late as the third to fourth week after the injection [8]. Thus, in clinical practice, the entire treatment process of CAR-T therapy requires close monitoring by the medical team to detect abnormalities in patients and to buy time to correct the series of toxicity caused by CAR-T cells.

4. Expectations

Although CAR-T therapy has many limitations to date, there is no doubt that it is still a promising therapeutic strategy that deserves continuous improvement and promotion. In recent years, many researchers have pointed out some areas where this newly emerging therapy needs to be improved.

First, many researchers have pointed out that the efficacy of this therapy can be improved by combining it with other therapeutic approaches. Data from a clinical trial on PD-1 and CAR-T cells

showed that the expansion and efficacy of CAR-T cells were significantly improved by the combination of PD-1-PD-L1 blockade [10]. Also, in the above-mentioned article examining antigen loss responses, Majzner and Mackall suggest that combination therapy has the potential to reduce antigen loss responses and thus reduce tumor recurrence after CAR-T therapy. Secondly, considering that culturing CAR-T cells takes a long time and numerous patient T-cell samples, future attempts could be made to adjust the in vitro cell culture conditions by changing the cytokine formulation conditions, thus reducing the culture time and prolonging the durability of CAR-T therapy [11]. Moreover, since T cell expansion, differentiation and survival are controlled by complex signaling responses of T cell receptors, scientists are now also considering the development of pharmacological inhibitors that activate or inhibit signaling pathways to enhance T cell survival [11].

5. Conclusion

The advent of CAR-T therapy is revolutionary in cancer treatment and can effectively improve the survival time and life quality of patients with R/R DLBCL. This therapy has many advantages that traditional oncology treatments do not have, such as high specificity, good detection of tumor cells, and ideal treatment outcome. Additionally, CAR-T has a wide range of applications, and is not limited to the treatment of DLBCL but can also be applied for the treatment of many other B-cell-related malignancies.

However, several drawbacks regarding CAR-T therapy still need to be addressed. These include post-treatment relapse caused by antigen loss and a range of toxic effects that may be associated with CAR-T cells. Many researchers have pointed the way to improve or address the shortcomings associated with CAR-T therapies. However, resolving the various limitations of CAR-T therapies is a lengthy process, which needs to be supported by substantial research studies, clinical experience, and data analysis. However, it is believed that with the efforts of many researchers, the major defects of CAR-T therapy will be solved and bring hope for survival to more cancer patients.

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